بسم الله الرحمن الرحيم

Sudan University of Science and Technology

College of Graduate Studies

Study of the Ideal Delay Period of Carbimazole for Hyperthyroidism Patients Using Thyroid Function Test

دراسة فترة التأخير المثالية للكاربيمازول لمرضى فرط نشاط الغدة الدرقية باستخدام اختبار وظائف الغدة الدرقية

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

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2019

الآية

يقول الله عز وجل:

بسم الله الرحمن الرحيم

وَتَوَكَّلْ عَلَى اللَّهِ وَكَفَى بِاللَّهِ وَكِيلًا

(3: سورة الأحزاب)

Dedication:

To my mother Salma Ali Alajab and my father Ahmed Abdullah Qurashi whom are the reason I am here today.

To my backbones Abdullah and Yousif, my leaning shoulders Yousra and Ethar, my lovely princess Dania and my charming knight Muaaz.

With love…

Acknowledgment:

My greatest gratitude to:

Prof. MOHAMED AL FADIL for kindly supervising this study and for his guiding through all the time that made this work possible.

I am thanking all the people in my life who loved me, believed in me and always supported me through my entire journey of life, specially while getting this degree.

Abstract:

This study consists of 51 hyperthyroid patients of different ages, gander, weight and heights whom were under different doses of medication (Carbimazole) and were referred to nuclear medicine department for thyroid scan to follow-up their response to medication by identifying the uptake of thyroid gland.

These patients were divided into three groups (A, B and C) depending on their Thyroid Hormone Test (TFT) results while using medication. Each group been stopped from their medication for a specific period (3, 5 and 7days), to check whether patient's thyroid hormone levels might elevate into a toxic level, and whether the accuracy of thyroid images would increase by increasing the delay period.

To measure the thyroid hormone levels, (TFT) been made for patients. Two blood samples had been taken from each patient, the first while they were still under medication, and the second was according to their group (A, B and C) which is after 3, 5 and 7 days respectively.

To check the accuracy of thyroid images, the patients underwent thyroid scan after a delay period of 3, 5 and 7 days respectively from medication. Images of thyroid uptake of the three groups were compared after the acquisition of thyroid scan has been made.

The study been conducted at Khartoum Oncology Hospital in Sudan, between (Dec2018-Dec2019). The results showed that an elevation of thyroid hormones occurs as the patient stops the medication, and it increases as the delay time increases. In addition, it showed no significant increasing in the accuracy of thyroid scan as the delay time increased, TFT was quite enough for determining patient's response to medication.

الخلاصة:

تتكون هذه الدراسة من 51 مريضا ممن يعانون فرط نشاط الغدة الدرقية من مختلف الأعمار، والوزن، والأطوال والذين كانوا يتعاطون جرعات مختلفة من الدواء (كاربيمازول) وتم إحالتهم إلى قسم الطب النووي لفحص الغدة الدرقية لمتابعة استجابتهم للعلاج من خلال تحديد امتصاص الغدة الدرقية.

تم تقسيم هؤلاء المرضى إلى ثلاث مجموعات (أ، ب، ج) اعتمادا على نتائج اختبار هرمون الغدة الدرقية (TFT) أثناء استخدام الدواء. تم إيقاف كل مجموعة من العلاج لفترة محددة (3 و5 و7 أيام)، للتحقق مما إذا كانت مستويات هرمون الغدة الدرقية لدى المريض قد ترتفع إلى مستوى سام، وما إذا كانت دقة صور الغدة الدرقية ستزداد عن طريق زيادة فترة التأخير.

لقياس مستويات هرمون الغدة الدرقية، تم إجراء فحص الهرمونات (TFT) للمرضى. تم أخذ عينتان دم من كل مريض، أولهما كان المريض لا يزال يخضع للعلاج، والثانية كان وفقًا لمجموعتها (أ، ب، ج) بعد 3 و5 و7 أيام على التوالي.

للتحقق من دقة صور الغدة الدرقية، خضع المرضى لفحص الغدة الدرقية بعد فترة الإيقاف 3 و 5 و 7 أيام على التوالي من الدواء. وتمت مقارنة صور امتصاص الغدة الدرقية للمجموعات الثلاث بعد إجراء عملية فحص الغدة الدرقية.

أجريت الدراسة في مستشفى الخرطوم لعلاج الأورام في السودان، بين (ديسمبر 2018 وديسمبر 2019). أظهرت النتائج أن ارتفاع هرمونات الغدة الدرقية يحدث عندما يتوقف المريض عن تناول الدواء، ويزيد كلما زاد زمن الإيقاف. بالإضافة إلى ذلك، لم تظهر زيادة ملحوظة في دقة فحص الغدة الدرقية مع زيادة وقت التأخير، وكان فحص الهرمونات TFT كافياً لتحديد استجابة المريض للعلاج.

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Introduction

Chapter One

1.1 Introduction

Several diseases may affect thyroid gland. Hyperthyroidism occurs when the gland produces excessive amounts of thyroid hormones, the most common cause being Graves' disease, an autoimmune disorder. Thyroid storm is a condition that occurs due to excessive thyroid hormone of any cause and therefore includes hyperthyroidism.

Treatment depends partly on the cause and severity of disease. There are three main treatment options: radioiodine therapy, medications, and thyroid surgery. Medications such as beta-blockers may control the symptoms, and anti-thyroid medications such as Carbimazole can help people temporarily or permanently depending on the severity of their condition.

The diagnosis of hyperthyroidism is confirmed by blood tests, which show a decreased thyroid-stimulating hormone (TSH) level and elevated T4 and T3 levels. TSH is a hormone made by the pituitary gland in the brain that tells the thyroid gland how much hormone to make. When there is too much thyroid hormone, the TSH will be low. Also a nuclear thyroid scan can confirm the diagnosis by showing the uptake of technetium-99m(^{99m}Tc) in thyroid gland. If the uptake was higher than 4%, it indicates hyperthyroidism disease.

Although the delivery of optimal patient care is the ultimate goal, cost-efficient utilization of limited resources is a growing concern. The goal of avoiding unnecessary use of expensive invasive procedures has focused more attention on the use of noninvasive or less invasive diagnostic and therapeutic modalities, including nuclear imaging. Ultimately, it is the treating physician responsibility to rationalize the utilization of resources for optimal patient care at reasonable cost.

1.2 Problem of the Study

Usually as a preparation for thyroid scan, a hyperthyroidism patient is being ordered to stop his medication (Carbimazole) for a period. It was noticed that the delay period of Carbimazole for these patients leads to an acute elevation of thyroid hormones that may end up as thyroid storm. Therefore if the co-factors that increase the effect are known then the estimation can be achieved and hence a reduction of the side effect is done.

1.3 Objective

1.3.1 General Objective

To study the ideal delay period of Carbimazole for hyperthyroidism patients using thyroid function test as the main cause of thyroid storm.

1.3.2 Specific Objectives

1. To correlate the duration of treatment with the first TFT results.
2. To correlate the dose of Carbimazole with the first TFT results.
3. To find the significance difference before and after the delay period.
4. To correlate TFT before and after the delay period with age, height, body mass index (BMI), period of delay and the dose of drug has been takin.
5. To estimate the result of the second TFT using the first TFT result, body characteristics, duration of the treatment and the delay of medication.
6. To correlate the accuracy of thyroid images with the delay period.

1.4 Significance of the Study

This study may estimate the ideal delay period that a hyperthyroidism patient can stop his medication without leading to any side effects. Knowing this period and correlate it with the co-factors that increase the effect will be a helpful factor for the performance of thyroid scan without any post side effects.

1.5 Thesis outline

This thesis falls into five chapters. Chapter One includes Introduction, Problem of the study, Objectives, Significance of the study and Thesis outline. Chapter Two contained Literature review and previous studies. Chapter Three includes Materials and Method. Chapter Four contain the result and Discussion. While Chapter Five includes Conclusion, Recommendation and References.

Chapter Two

Theoretical background and Literature review

Chapter Two

Theoretical background and Literature review

2.1 Theoretical background

2.1.1 Thyroid gland

The thyroid gland is an endocrine gland in the neck, consisting of two lobes connected by an isthmus. It is found at the front of the neck, below the Adam's apple. The thyroid gland secretes thyroid hormones, which primarily influence the metabolic rate and protein synthesis. The hormones also have many other effects including those on development. The thyroid hormones triiodothyronine (T3) and thyroxine (T4) are created from iodine and tyrosine. Hormonal output from the thyroid is regulated by thyroid-stimulating hormone (TSH) secreted from the anterior pituitary gland, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus.

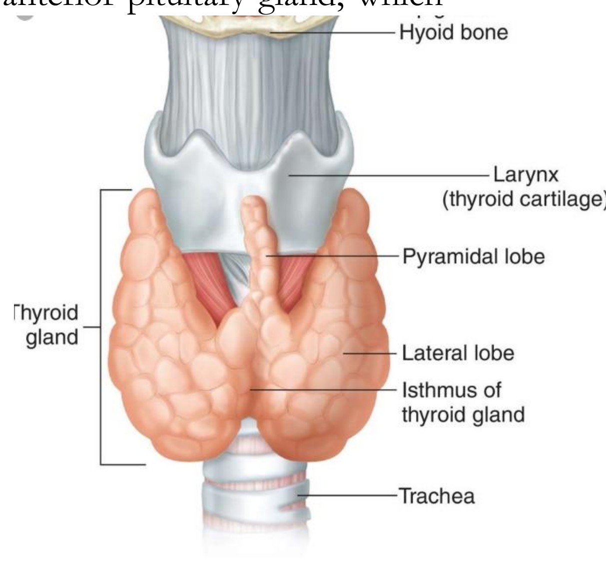


Figure 2.1: anatomical details of thyroid

2.1.1.1 Anatomical Variations

Hypoglossal Duct Cyst Thyroglossal duct fails to involute completely.

A thyroid Absence of Thyroid gland:

Pyramidal Lobe , Absence of Isthmus and Ectopic Gland

The average gland is 40 to 60 mm in length and 13 to 18 mm thick with the isthmus approximately 4 to 6 mm thick. A pyramidal lobe is present in 10% to 40% of it is a finger-like lobe of tissue which extends superiorly from the isthmus and is of variable height. The normal thyroid gland has a wide range of sizes. Normal variations in size occur with age, gender and nutrition: the gland is larger in youth, the well-nourished and in women - especially during menstruation and pregnancy.

2.1.1.2 Thyroid tissue:

The microscopic structure of the thyroid is quite distinctive. Thyroid epithelial cells - the cells responsible for synthesis of thyroid hormones - are arranged in spheres called thyroid follicles. Follicles are filled with colloid, a proteinaceous depot of thyroid hormone precursor.

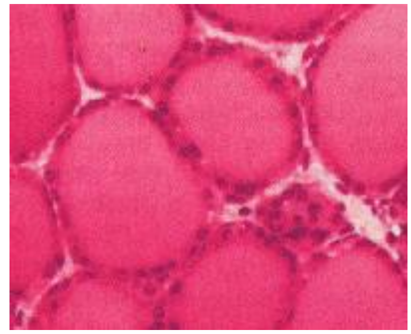


Figure 2.2: Thyroid tissue

In addition to thyroid epithelial cells, the thyroid gland houses one other important endocrine cell. Nestled in spaces between thyroid follicles are Para follicular or C cells, which secrete the hormone calcitonin. The structure of a parathyroid gland is distinctly different from a thyroid gland. The cells that synthesize and secrete parathyroid hormone are arranged in rather dense cords or nests around abundant capillaries. (Chwajink, 1995)

2.1.1.3 Physiology of the thyroid gland:

The thyroid gland located immediately below the larynx on each lobe of and anterior to the trachea, is one of the largest endocrine glands, normally weighting 15 to 20 grams in adults. The thyroid secrete two major hormones, thyroxin T4 and triiodothyroxine T3,. Both of these hormones profoundly increase the metabolic rate of the body. Complete lack of thyroid secretion usually causes the basic 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 thyroid pituitary gland. The thyroid gland also secretes calcitonin, an important hormone for calcium metabolism (Stathatos, 2012).

Synthesis and Secretion of the Thyroid Metabolic Hormone About 93 percent of the metabolically active hormones secreted by the thyroid gland is thyroxin, and 7 percent triiodothyroxine. However, almost all the thyroxin is eventually converted to triiodothyronine in the tissue, 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. Triode threonine is about four times as potent as thyroxin, but it's present in the blood in much smaller quantities and persists for much shorter time than thyroxin. (Moleti et al., 2014). Iodide Trapping is the first stage in the formation of thyroid hormone, it 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 anterior of the cell. This is called iodide trapping. In 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. (Moleti et al., 2014).

Oxidation of the iodide ion is the first essential step in the formation of the thyroid hormone is conversion of the iodide ions to oxidized form iodine, either nascent iodine (10) or (13). That is then capable of combining directly with the amino acid tryosine. This oxidation of iodine is promoted by the enzyme peroxidase and its accompanying hydrogen peroxide, which provide potent system capable of oxidizing iodides. 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. (Moleti et al., 2014).

The binding of iodine with the thyroglobulin molecule is called organification of the thyrogloulin. Oxidized iodine even in the molecular form will bind directly but very slowly with the amino acid tyrosine. In the thyroid cell, however, the oxidized iodine is associated with an iodinates. Enzyme the process to occur within seconds or minute.

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, the stage of iodination of tyrosine and final formation of the two important thyroid hormones, thyroxine and triiodothyronine. (Mariotti and Beck-Peccoz, 2000).

Release of thyroxine and triiodothyronine from the thyroid Gland: Throglobulin itself is not released into the circulating blood in measurable amounts, instead, thyroxine and triiodothyronine must first be cleaved from the thyroglobulin molecule, and then these free hormones are released.

Daily Rate of Secretion of Thyroxine and Triiodothyronine about 93 per cent of thyroid hormone released from the thyroid gland is normally thyroxine and only 7 percent is triiodothyronine, about 35 micrograms of triiodothyronine per day.

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, the new result is generalized increase in functional activity throughout the body. (Mariotti and Beck-Peccoz, 2000).

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 animals body increase in size as well as number. Furthermore, the total membrane surface area of the mitochondria increases almost directly in proportion of the increased metabolic rate of the whole animal. Therefore, one the principal functions of the thyroxine might be increases the rate of formation of adenosine triphosphate (ATP) to energize cellular function. However, the increase in the number and activity of the cell as well as the cause of the increase. (Mariotti and Beck-Peccoz, 2000).

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+-Ka+-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 fact, thyroid hormone also causes the cell membrane of most cells to become leaky to sodium ions, which further activate the sodium pump and further increases heat production.

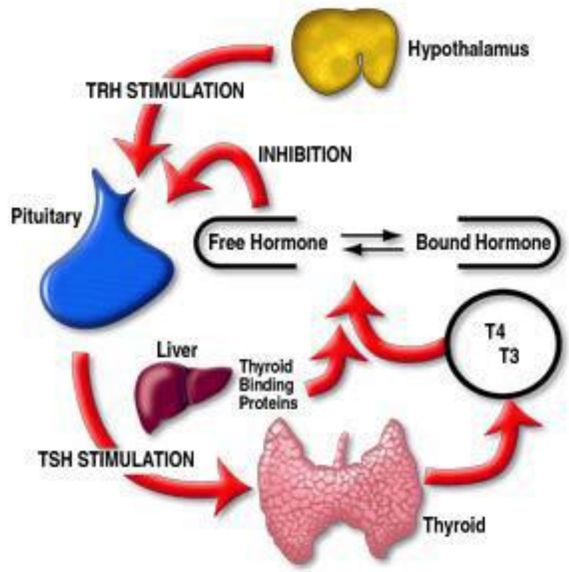


Figure 2.3 Thyroid Function

2.1.1.4 Pathology of the thyroid:

Goiter: Any form of thyroid enlargement is called a goiter. The increase in volume is gradual and may be associated with normal thyroid function (euthyroid), decreased function (hypothyroidism) or increased hormonal production (hyperthyroidism). Euthyroid goiter is the most common and iodine deficiency is usually the cause (Cignini et al., 2012).

Nodules: Many thyroid diseases can present with one or more thyroid nodules. Benign thyroid nodules outnumber malignant thyroid nodules approximately 500 to 1.

Solitary thyroid nodules: There are several characteristics of solitary nodules of the thyroid which make them suspicious for malignancy. Although as many as 50% of the population will have a nodule somewhere in their thyroid, the overwhelming majority of these are benign. Occasionally, thyroid nodules can take on characteristics of malignancy and require either a needle biopsy or surgical excision.

Diffuse Colloid (Simple) Goiter: Zones of glandular hyperplasia result in dilated follicles filled with colloid. These dilated follicles appear as cold nodules. They can undergo hemorrhage and necrosis. Colloid nodules are the most common type of thyroid nodule but thyroid function is normal.

Sonographically; the gland is symmetrically enlarged with normal echogenicity.

Adenomatous or Multinodular Goiters (MNG): Sometimes hyperplasia and dilatation of follicles with colloid does not affect the thyroid uniformly and results in a multinodular goiter. Thyroid function is usually normal. The patient presents with an enlarged gland and pressure symptoms related to the trachea and esophagus. Multiple cold nodules are demonstrated on NM scans. MNG's can grow to enormous sizes and are often asymmetrical due to nodule masses of various sizes (Cignini et al., 2012).

Hyperthyroidism: Hyperthyroidism means too much thyroid hormone. Current methods used for treating a hyperthyroid patient are radioactive iodine, anti-thyroid drugs, or surgery. Each method has advantages and disadvantages and is selected for individual patients. Many times the situation will suggest that all three methods are appropriate, while other circumstances will dictate a single best therapeutic option. Surgery is the least common treatment selected for hyperthyroidism. There are different causes of hyperthyroidism but the most common underlying cause of hyperthyroidism is Graves' disease.

There are actually three distinct parts of Graves' disease:

Over activity of the thyroid gland (hyperthyroidism), Inflammation of the tissues around the eyes causing swelling, and Thickening of the skin over the lower legs (pretibial myxedema)

Characteristics of Graves' Disease: Graves' Disease effects women much more often than men (about 8.1 ratio, thus 8 women get Graves' Disease for every man that gets it. Graves' Disease is often called diffuse toxic goiter because the entire thyroid gland is enlarged, usually moderately enlarged, and sometimes quite big. Graves' Disease is uncommon over the age of 50 (more common in the 30's and 40's). Graves' Disease tends to run in families (Cignini et al., 2012).

Hypothyroidism: Hypothyroidism means too little thyroid hormone and is a common problem. In fact, hypothyroidism is often present for a number of years before it is recognized and treated. There are two fairly common causes of hypothyroidism:

The first is a result of previous (or currently ongoing) inflammation of the thyroid gland which leaves a large percentage of the cells of the thyroid damaged (or dead) and incapable of producing sufficient hormone. The most common cause of thyroid gland failure is called autoimmune thyroiditis (also called Hashimoto's thyroiditis), a form of thyroid inflammation caused by the patient's own immune system.

The second major cause is the broad category of medical treatments.

Hypothyroidism can even be associated with pregnancy. Treatment for all types of hypothyroidism is usually straightforward.

Symptoms of Hypothyroidism: They are many symptoms of hypothyroidism: Fatigue, weakness, weight gain or increased difficulty losing weight, coarse, dry hair, dry, rough pale skin, hair loss, cold intolearance (can't tolerate the cold like those around you), muscle cramps and frequent muscle eaches, constipation, depression, irritability, memory loss, abnormal menstrual cycles and decreased libido.

Thyroiditis: Thyroiditis is an inflammatory process ongoing within the thyroid gland. Thyroiditis can present with a number of symptoms such as fever and pain, but it can also present as subtle findings of hypo or hyper-thyroidism. There are a number of causes, some more common than others. Thyroiditis is an inflammation (not an infection) of the thyroid gland. Several types of thyroiditis exits and the treatment is different for each (NIDDK et. al., 2013).

2.1.2 Hyperthyroidism

Hyperthyroidism is the condition that occurs due to excessive production of thyroid hormones by the thyroid gland. Signs and symptoms vary between people and may include irritability, muscle weakness, sleeping problems, a fast heartbeat, heat intolerance, diarrhea, enlargement of the thyroid, hand tremor, and weight loss. Symptoms are typically less severe in the elderly and during pregnancy. An uncommon complication is thyroid storm in which an event such as an infection results in worsening symptoms such as confusion and a high temperature and often results in death (NIDDK et. al., 2013).

Graves' disease is the cause of about 50% to 80% of the cases of hyperthyroidism. Other causes include multinodular goiter, toxic adenoma, inflammation of the thyroid, eating too much iodine, and too much synthetic thyroid hormone. A less common cause is a pituitary adenoma. The diagnosis may be suspected based on signs and symptoms and then confirmed with blood tests. Typically blood tests show a low thyroid stimulating hormone (TSH) and raised T3 or T4. Nuclear medicine thyroid scan may help determine the cause (NIDDK et. al., 2013).

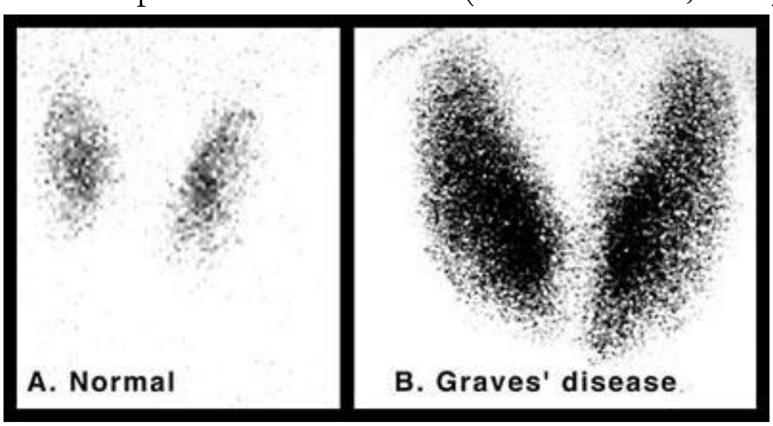
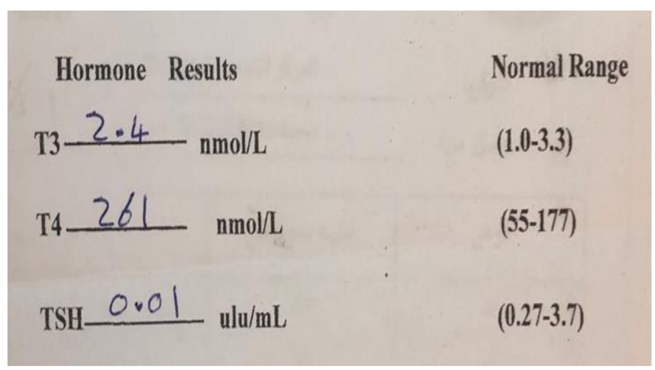


Figure 2.3 A. thyroid scan uptake of a normal patient vs. B. thyroid scan uptake of a hyperthyroidism patient



Hormone	Results		Normal Range
T3	2.4	nmol/L	(1.0-3.3)
T4	261	nmol/L	(55-177)
TSH	0.01	ulu/mL	(0.27-3.7)

Figure 2.4 TFT hyperthyroidism result

Treatment depends partly on the cause and severity of disease. There are three main treatment options: radioiodine therapy, medications, and thyroid surgery. Radioiodine therapy involves taking iodine-131 by mouth, which is then concentrated in and destroys the thyroid over weeks to months. Medications such as beta-blockers may control the symptoms, and anti-thyroid medications such as Carbimazole may temporarily help people while other treatments are having effect. Surgery to remove the thyroid is another option. This may be used in those with very large thyroids or when cancer is a concern. It occurs between two and ten times more often in women (Markovic V, Eterovic D et. al., 2007)

2.1.3 Carbimazole

Carbimazole is a pro-drug as after absorption it is converted to the active form, methimazole. Methimazole prevents thyroid peroxidase enzyme from coupling and iodinating the tyrosine residues on thyroglobulin, hence reducing the production of the thyroid hormones T3 and T4 (thyroxine). It's a medical therapy for hyperthyroidism typically involves either titrating the dose of Carbimazole until the patient becomes euthyroid or maintaining a high dose of Carbimazole to suppress endogenous thyroid production, and then replacing thyroid hormone with levothyroxine ("block and replace"). Treatment is usually given for 18–24 months followed by a trial withdraw. The onset of anti-thyroid effect is rapid but the onset of clinical effects on thyroid hormone levels in the blood is much slower. This is because the large store of pre-formed T3 and T4 in the thyroid gland and bound to thyroid binding globulin (99% bound) has to be depleted before any beneficial clinical effect occurs. The active moiety, occur at 1 to 2 hours. Carbimazole has a half-life of 5.3 to 5.4 hours. (Bahn RS et. al. 2009).

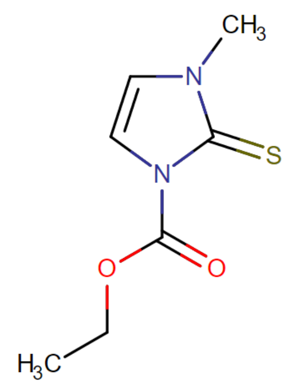


Figure 2.5 Carbimazole chemical structure

2.1.4 T3, T4 and TSH

2.1.4.1 T3

Triiodothyronine, also known as T3, is a thyroid hormone. It affects almost every physiological process in the body, including growth and development, metabolism, body temperature, and heart rate.

Production of T3 and its prohormone thyroxine (T4) is activated by thyroid-stimulating hormone (TSH), which is released from the anterior pituitary gland. This pathway is part of a closed-loop feedback process: Elevated concentrations of T3, and T4 in the blood plasma inhibit the production of TSH in the anterior pituitary gland. As concentrations of these hormones decrease, the anterior pituitary gland increases production of TSH, and by these processes, a feedback control system stabilizes the amount of thyroid hormones that are in the bloodstream.

The half-life of T3 is about 2.5 days. (Bowen R. et. al., 2010).

2.1.4.2 T4

Thyroxine also known as (T4) produced and released by the thyroid gland. It's a tyrosine-based hormone that is primarily responsible for regulation of metabolism. T3 and T4 are partially composed of iodine. A deficiency of iodine leads to decreased production of T3 and T4, enlarges the thyroid tissue and will cause the disease known as simple goitre. The major form of thyroid hormone in the blood is thyroxine (T4), which has a longer half-life than T3, The half-life of T4 is about 6.5 days. In humans, the ratio of T4 to T3 released into the blood is approximately 14:1. T4 is converted to the active T3 (three to four times more potent than T4) within cells by deiodinases (5'-iodinase). (Bowen R. et. al., 2010).

2.1.4.3 TSH

Thyroid-stimulating hormone (also known as thyrotropin, thyrotropic hormone, or abbreviated TSH) is a pituitary hormone that stimulates the thyroid gland to produce (T4), and then (T3) which stimulates the metabolism of almost every tissue in the body. It is a glycoprotein hormone produced by thyrotrope cells in the anterior pituitary gland, which regulates the endocrine function of the thyroid. TSH (with a half life of about an hour) stimulates the thyroid gland to secrete the hormone thyroxine (T4), which has only a slight effect on metabolism. TSH is secreted throughout life but particularly reaches high levels during the periods of rapid growth and development, as well as in response to stress. The concentration of thyroid hormones (T3 and T4) in the blood regulates the pituitary release of TSH; when T3 and T4 concentrations are low, the production of TSH is increased, and, conversely, when T3 and T4 concentrations are high, TSH production is decreased.

The finding of an elevated TSH and low FT4 or FTI indicates primary hypothyroidism due to disease in the thyroid gland. A low TSH and low FT4 or FTI indicates hypothyroidism due to a problem involving the pituitary gland. A low TSH with an elevated FT4 or FTI is found in individuals who have hyperthyroidism. (Bowen R. et. al., 2010).

2.1.5 TFT

The best way to initially test thyroid function is to measure the TSH level in a blood sample. Changes in TSH can serve as an "early warning system" – often occurring before the actual level of thyroid hormones in the body becomes too high or too low. Thyroid function tests are a series of blood tests used to measure how well thyroid gland is working. Available tests include the T3, T3RU, T4, and TSH. The usual blood tests done for thyroid function are TSH, T4 and sometimes T3. A blood sample is taken from a vein in the arm and sent off to the laboratory for analysis. Usually the 'free' or active portion of T4 and T3 is measured (i.e., FT4 and FT3). Typical reference ranges for healthy adults are:

Test	From	To	Units
TSH	0.4	4.0	mU/l (milliunits per litre)
T4	55	177	nmol/l (nanomoles per litre)
T3	1.0	3.3	nmol/l (nanoomoles per litre)

Table 2.2: Normal result for Thyroid Function Test.

In pregnancy the serum TSH reference range is different from the general population and should ideally be based on reference ranges derived from healthy pregnant women in the same population.

Interpreting these tests, together with symptoms, in order to diagnose whether a person have a thyroid disorder, how severe it is, and how to treat it.

T4 is the main form of thyroid hormone circulating in the blood. A Total T4 measures the bound and free hormone and can change when binding proteins differ (Dayan CM et. al., 2001).

2.1.5.1 TSH and T4

- If the TSH level is high and the T4 result is low this suggests an underactive thyroid (hypothyroidism) that requires treatment.
- If the TSH level is low and the T4 result is high this suggests an overactive thyroid (hyperthyroidism) that requires treatment.
- If the TSH level is slightly raised but the T4 level is still within the normal reference range this is called subclinical hypothyroidism or mild thyroid failure.

- A low TSH with a low T4 may be a result of a failure of the pituitary gland (secondary hypothyroidism caused by hypopituitarism) or a response to a significant non-thyroid illness.

2.1.5.2 T3

T3 tests are often useful to diagnosis hyperthyroidism or to determine the severity of the hyperthyroidism. Patients who are hyperthyroid will have an elevated T3 level. In some individuals with a low TSH, only the T3 is elevated and the FT4 or FTI is normal. T3 testing rarely is helpful in the hypothyroid patient, since it is the last test to become abnormal. Patients can be severely hypothyroid with a high TSH and low FT4 or FTI, but have a normal T3. (Dayan CM et. al., 2001).

2.1.6 Thyroid scan

A thyroid scan is a specialized imaging procedure for examining thyroid. Typically, the scan works to evaluate the way thyroid functions. This scan involves using small amounts of radioactive (^{99m}Tc) material to diagnose disease.

A radioactive material called a radioisotope, or radionuclide "tracer," is given before the test through an injection. The tracer releases gamma rays when it's in the body. A gamma camera or scanner can detect this type of energy from outside the body.

The camera scans thyroid area. It tracks the tracer and measures how thyroid processes it. The camera works with a computer to create images that detail the thyroid's structure and function based on how it interacts with the tracer.

A thyroid scan can be used to evaluate abnormalities found in a physical exam or laboratory test. The images from this test can be used to diagnose:

Lumps, nodules (cysts), or other growths, Inflammation or swelling, Hyperthyroidism, Hypothyroidism, Goiter, which is an abnormal enlargement of the thyroid and Thyroid cancer

During a thyroid scan, a radioactive substance called a tracer (^{99m}Tc) is injected into a vein in the arm. The tracer travels through your bloodstream and into thyroid gland. Then a special camera takes images of the tracer in thyroid gland while ^{99m}Tc being trapped inside the gland.

2.1.6.1 Benefits

- It provides unique information—including details on the function and anatomy of thyroid—that is often unattainable using other imaging procedures.
- It is less expensive and may yield more precise information than exploratory surgery.

2.1.6.2 Risks

- Because only a small dose of radiotracer is used, thyroid scan have a relatively low radiation exposure. This is acceptable for diagnostic exams. Thus, the radiation risk is very low when compared with the potential benefits.
- Allergic reactions to radiotracers are extremely rare and usually mild.
- Injection of the radiotracer may cause slight pain and redness. This should rapidly resolve.
- Thyroid scan is not performed on patients who are pregnant because of the risk of exposing the fetus to radiation. These tests are also not recommended for breastfeeding women.

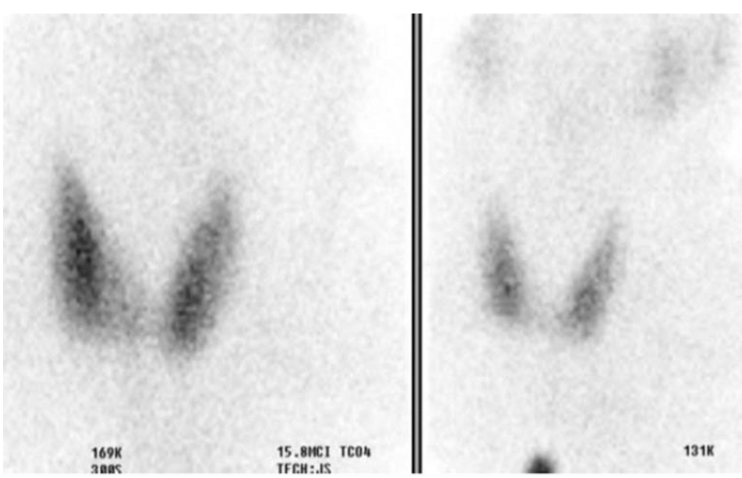


Figure 2.6 Normal 99mTc thyroid scan. Symmetric, homogeneous uptake with less intense salivary gland uptake and only mild background uptake. The inferior activity is due to a 57Co marker at the suprasternal notch.

2.2 Literature review

- Walter MA, Christ-Crain M, Müller B, Müller-Brand J. et al(2007). Compared radioiodine uptake and thyroid hormone levels on or off simultaneous carbimazole medication; a prospective paired comparison. The aim was to allow radioiodine (RAI) treatment in patients with need for anti-thyroid drug medication and low RAI uptakes we investigated the feasibility of discontinuing carbimazole for 3 days to enhance the RAI uptake without concurrent exacerbation of hyperthyroidism. The method was prospectively investigated RAI dynamics and thyroid hormone concentration in 12 patients with low RAI uptake (<30%) under simultaneous carbimazole medication and 3 days after discontinuation. At both time points FT4, T3 and TSH were monitored. The result showed that discontinuation of carbimazole for 3 days led to a significant increase of RAI uptake in all patients. We found an enhancement up to 4.9-fold compared to the measurement on carbimazole. The mean RAI uptake increased from 15.2 +/- 4.4% to 50.1 +/- 15.5% (p<0.001). The intrapersonal radioiodine half-life increased from 4.2 +/- 1.6 days to 5.4 +/- 0.7 days (p = 0.13). Mean thyroid hormone concentration was not affected by the three day withdrawal of anti-thyroid drugs and no patient suffered from an aggravation of biochemical hyperthyroidism. The conclusion was a withdrawal of carbimazole for 3 days is long enough to provide sufficiently high RAI uptakes for RAI treatment in patients with low RAI uptakes and short enough to avoid the risk of exacerbation of hyperthyroidism.

- M. Faruk Hossain. et al.(2017). Correlated Serum T4, T3 and TSH Levels with Radioiodine Thyroid Uptakes. 240 studies including serum T4, T3, TSH and thyroid uptake at 2 and 24 hrs. were performed in 48 Bangladeshi adult individuals (52% female and 48% male). The aim of the present study was to make a correlation between thyroid serum levels and radioiodine thyroid uptake values of same individuals. Serum T4 and T3 were assessed with commercially available radioimmunoassay kits and TSH with a highly sensitive immunoradiometric assay kits (Beijing Atom Hightech Co. Ltd., China). The uptake study was consisted of oral administration of 6 – 10 μCi of 131I as sodium-iodide. Correlation coefficients (r) were calculated and tested for statistical significance. Radioiodine thyroid uptake values measured in this study show a statistically significant positive correlation with T4 and T3 levels and negative correlation with serum TSH levels. The present results were also compared with the experimental data available in literature and found to be in fairly good agreement. Conclusion: A total of 48 adult patients including 25 female and 23 male, referred to the Institute of Nuclear Medicine and Allied Sciences (INMAS), Dhaka for thyroid function tests were evaluated to study the correlation of serum T4, T3, TSH levels with 24 and 2 hrs. thyroid RAIU values. The present results revealed a positive and statistically significant correlation of serum T4 and T3 levels with RAIU values. Serum TSH levels, on the other hand, showed an expected negative correlation with uptake values. The results obtained in this study were also found to be in fairly good agreement with the reported data. However, the positive correlation of serum T4 and T3 RIA values with 24 and 2 hrs RAIU, in this study, is not a perfect one because correlation coefficient (r) though greater than zero ($r > 0$) is less than one ($r < 1$). The present study, therefore, suggests that thyroid RAIU cannot be recommended as the sole diagnostic investigation for thyroid function tests.

- ❖ Walter MA, Christ-Crain M, Schindler C, Müller-Brand J, Müller B. et al.(2010). Studied outcome of radioiodine therapy without, on or 3 days off carbimazole: a prospective interventional three-group comparison. Carbimazole ameliorates hyperthyroidism but reduces radioiodine uptake and adversely affects the outcome of simultaneous radioiodine therapy. We explored whether withdrawal of carbimazole for 3 days can restore the outcome of radioiodine treatment without concurrent exacerbation of hyperthyroidism. By generating three groups with comparable radioiodine uptake, we also investigated whether the effect of carbimazole depends on the radioiodine uptake.

  The method was Stratified by a radioiodine uptake >30%, 227 consecutive adult patients were prospectively assigned to radioiodine therapy (target dose 200 Gy) without, on or 3 days off carbimazole. Patients were clinically (Crooks-Wayne score) and biochemically T3, FT4, TSH followed up after 3, 6 and 12 months. Primary endpoint was outcome 12 months after radioiodine therapy. The results was a total of 207 patients completed follow-up (toxic nodular goitre, n=117; Graves' disease, n=90). The overall success rate was 71.5%. Patients without and 3 days off carbimazole had similar biochemical (81.4% and 83.3%, respectively; $p=0.82$) and clinical outcomes [median (range) Crooks-Wayne score 0 (0-16) and 1 (0-10), respectively; $p=0.73$], which were both higher than in patients on carbimazole [42.6%, $p<0.001$; Crooks-

Wayne score 3 (0-30), p<0.03]. Time to achieve cure was delayed on carbimazole. No changes in thyroid hormone levels occurred after 3 days' discontinuation of carbimazole. Logistic regression revealed that all observed cure rates were independent of entity, sex, age, thyroid volume, radioiodine uptake, radioiodine half-life, FT4, T3 and TSH. The conclusion: Patients under carbimazole treatment can be referred for radioiodine therapy after withdrawal of carbimazole for only 3 days. Three days of carbimazole withdrawal is long enough to restore the success of radioiodine therapy and short enough to avoid the risk of exacerbation of hyperthyroidism.

- Bhattarai R., Dhakal B., Jyothinagaram S. et al.(2013). Discussed thyroid storm with fatal multi organ failure. Thyroid storm is an endocrine emergency with high mortality rate. Cases of fatal multi organ failure due to thyroid storm are rarely reported. A 52 years old female with Graves' disease on methimazole, was switched to Propylthiouracil (PTU) due to severe skin rash. She developed jaundice on PTU, and was referred to us. She had tachypnea, tachycardia, and icterus. Thyroid was enlarged, soft and non-tender. Blood work revealed TSH at <0.01 mIU/L (0.45–4.50), Free T4 (FT4) at >8 ng/dl (0.8-1.7), positive TSI at 362% (< 140), elevated total bilirubin at 7.1 mg/dl (0.2–1.3), elevated AST 58 IU/L (10–41) with normal ALT and ALP, and elevated INR. Liver imaging was unremarkable. PTU induced hepatitis was suspected and PTU was discontinued. Propranolol and potassium iodide were started. Her clinical condition rapidly deteriorated with altered mental status, hypotension, and respiratory distress, requiring intubation and vasopressors support. Echocardiogram showed reduced EF 15–20%. Total bilirubin elevated at 21.6 mg/dl, AST at 7043 IU/L, ALT at 1802 IU/L. FT4 remained elevated with suppressed TSH. With the diagnosis of thyroid storm and multi organ failure, IV steroids, SSKI and cholestyramine were started. She was clinically unstable for thyroidectomy, and emergent plasmapheresis was done. However, patient developed DIC and GI bleeding. Despite aggressive management, her condition deteriorated, so, end of life care was pursued, and the patient expired. Thyroid storm is an acute, life-threatening condition caused by excessive release of thyroid hormones with an incidence of 1–2% among patients with hyperthyroidism, and the mortality of 10–30%. Graves' disease is the most common cause of thyroid storm, and often precipitated by abrupt cessation of antithyroid therapy as in our case. Thyroid storm is a clinical diagnosis based on presence of severe life threatening symptoms in a patient with laboratory evidence of elevated FT4, FT3 and suppressed TSH. Early recognition and treatment can avoid morbidity and mortality. When diagnosis of thyroid storm is strongly suspected, one should rapidly initiate effective life-saving treatment in the ICU. However, despite aggressive treatment thyroid storm can be fatal.

- Manouchehr N, Soraya A. et al.(2017). Predicted relapse from hyperthyroidism following antithyroid medication withdrawal using technetium thyroid uptake scanning. Objective: Technetium thyroid uptake (TTU) is not inhibited by antithyroid drugs (ATD) and reflects the degree of thyroid stimulation. We intended to predict the relapse rate from hyperthyroidism based on TTU measurement. Methods: Out of 44 initially enrolled subjects, 38 patients aged 41.6 ± 14.6 with Graves disease (duration: 84 ± 78 months) completed the study. TTU was performed with 40-second imaging of the neck and mediastinum 20 minutes after injection of 1 mCi technetium-99m pertechnetate. TTU was measured as the percentage of the count of activity accumulated in the thyroidal region minus the mediastinal background uptake to the count of 1 mCi technetium-99m under the same acquisition conditions. Then methimazole was stopped and patients were followed. The optimal TTU cutoff value for Graves relapse prediction was calculated using Youden's J statistic. Results: Hyperthyroidism relapsed in 11 (28.9%) patients 122 ± 96 (range: 15–290) days post-ATD withdrawal. The subjects in remission were followed for 209 ± 81 days (range: 88–390). TTU was significantly higher in patients with forthcoming relapse (12.0 ± 8.0 vs. 3.9 ± 2.0, P = .007). The difference was significant after adjustment for age, sex, history of previous relapse, disease duration, and thyroid-stimulating hormone (TSH) levels before withdrawal. The area under the receiver operative characteristic (ROC) curve was 0.87. The optimal TTU cutoff value for classification of subjects with relapse and remission was 8.7 with sensitivity, specificity, and positive and negative predictive value of 73%, 100%, 100%, and 90%, respectively (odds ratio [OR] = 10.0; 95% confidence interval [CI]: 3.4–29.3). Conclusion: TTU evaluation in hyperthyroid patients receiving antithyroid medication is an accurate and practical method for predicting relapse after ATD withdrawal.

- Zakavi SR, Khazaei G, Sadeghi R, Ayati N, Davachi B, Bonakdaran S, Jabbari Nooghabi M, Moosavi Z. et al.(2015). Methimazole discontinuation before radioiodine therapy in patients with Graves' disease. The aim of this clinical trial is to study the effect of three different time points of MMI discontinuation on response to RIT. Method and patients: Overall, 151 patients (18-65 years old), with Graves' disease who were taking MMI and referred to I-131 therapy, were consecutively assigned to one of three groups, and MMI was discontinued for 24-48, 48.1-72, and 72.1-168 h in group, 1, 2, and 3, respectively. Radioiodine uptake was measured in all patients and the radioiodine dose was calculated according to the Quimby formula to deliver 7.4 MBq of I-131 per gram of thyroid weight. Response to RIT was assessed at 1, 3, 6, and 12 months after RIT. Results: A total of 102 women and 49 men were included in the study. The mean administered dose of I-131 was 362.9±188.7 MBq (9.8±5.1 mCi) and the mean time to response for radioiodine was 4.1±3.6 months. There was no significant difference between the three groups in age, thyroid weight, anti-TPO level, radioactive iodine uptake level, and radioiodine dose ($P>0.1$). Response to RIT at 1, 3, 6, and 12 months after administration was also not different between the three groups ($P>0.57$). Conclusion: No difference was found in the response to treatment between patients with MMI discontinuation for 24-48, 48.1-72, and 72.1-96 h before RIT. Shorter discontinuation of MMI before RIT may be preferable in most patients.

- C Shivaprasad, KM Prasanna. et al.(2015). Studied Long-term carbimazole pretreatment reduces the efficacy of radioiodine therapy. : Data from several studies suggest that pretreatment with antithyroid drugs (ATD) before ^{131}I increases the risk of treatment failure. This effect has been demonstrated more consistently with propylthiouracil than with carbimazole (CMZ) or methimazole (MMI). Men with Graves' disease (GD) have a lower rate of remission with ^{131}I compared to women and the impact of long-term ATD pretreatment on the success of ^{131}I is unknown. The objective of our study was to compare the efficacy of fixed doses of radioiodine between patients with and without long-term CMZ pretreatment. Materials and Methods: We performed a retrospective study on 335 male patients with GD treated with ^{131}I from 1998 to 2008. 148 patients had been pretreated with CMZ, and the remaining 187 patients received 131 I without pretreatment. We compared the success rate of a single dose of ^{131}I, between patients with and without long-term CMZ pretreatment. Results: The success rate of a single dose of ^{131}I was significantly higher in patients without pretreatment than in patients who were pretreated with CMZ (91.4% vs. 82.3%, $P = 0.01$). The rate of hypothyroidism in the first 6 months after 131 I therapy was significantly higher in patients without pretreatment (55.1% vs. 44.6%, P = 0.05). There was also a trend for higher cumulative rate of hypothyroidism at last follow-up in non-pretreated patients (78.1% vs. 69.7%). Conclusion: Male patients with Graves' hyperthyroidism pretreated with CMZ have lower efficacy with ^{131}I therapy compared to non-pretreated patients. CMZ pretreatment given for a prolonged period reduces the efficacy of ^{131}I therapy.

- Farshid G, Gholamreza P, Mehrdad E, Kasra B, Aida K, Maryam S. et al.(2012). Studied the effect of methimazole on thyroid gland uptake of technetium in hyperthyroid patients. The aim of this study was to investigate the effect of methimazole on Technetium-99m reabsorbing by thyroid gland , it may be possible to perform thyroid scan when the patients are on the methimazole, this can be time saving and decrease the adverse effects of discontinuing methimazole. Patients and Methods: among all the patients with hyperthyroidism who referred to nuclear medicine ward of Shiraz University of medical sciences, 50 patients were randomly selected. We asked the patients who were on Methimazole, to discontinue the usage of all drugs (not Methimazole) and food that are effective on thyroid gland for 1 week, after that thyroid scan was performed for these patients. In the other episode, we asked them to discontinue the usage of all drugs (also Methimazole) and foods which are effective on thyroid gland for 1 week and then thyroid scan was performed again. Revealed data was analyzed under supervision of statistical specialist with descriptive methods on SPSS. Results: 34 patients were males (68%) and other was females. Mean age of the patients was 53.5 years. (Min: 39 years and max: 75 years). Although The ROI (Region of Interest) of thyroid was increased in the patients who used methimazole before scan 398.72(SD: 191.73) than the patients who discontinued for one week 380.15 (SD: 112.49), but the difference was not statistically significant. The ROI of peripheral tissue of the thyroid was decreased in the patients who used methimazole before scan 26.44(SD: 5.42) than the patients who discontinued for one week 27.0414 (SD: 5.57), but the difference wasn't statistically significant. Discussion: In conclusion, we demonstrated that methimazole pretreatment does not interfere with either the efficacy of ROI and reabsorbing of Technetium-99m in thyroid gland and peripheral tissues. A possible limitation of this study is the number of patients in the sample. So it seems that it may be possible to perform thyroid scan when the patients are on the methimazole, this can be time saving and decrease the adverse effects of discontinuing methimazole.

- Hadeel S. et al.(2017). Studied of Normal Thyroid Uptake using Technisium-99m. Thyroid gland is a vital endocrine gland in the body, estimation of its uptake and thyroid area are generally consider to be an important in several pathologic situations such as iodine deficiency, Goiter, thyroiditis, multi-nodular goiter and others. The aim of this study was to evaluate the normal range of thyroid uptake and determine the thyroid area in patients who has normal thyroid function test (T.F.T) and homogenous distribution of the radiotracer in Sudanese especially in Radiation & Isotope Center of Khartoum (RICK). This study includes 58 patients (91.5% Female, 8.5% Male) in different age, sex, center of origin and type of food and drink intake. For six months from Dec 2016 to May 2017. The most frequency of ages distribute as (25-35=31.03%, 15-25=29.3%), The thyroid uptake value in the gamma camera (mediso). The result of the study showed that the mean age was 33.6 $\pm$ 11 years old, the overall mean area of thyroid gland was 19.3 $\pm$ 3.78 cm^2. The mean area of right lobe was 7.7 $\pm$ 1.65 cm^2. The mean area of left lobe was 7.1 $\pm$ 1.84 cm^2. The right lobe area was significantly homogenous from left lobe area. Furthermore, a significant correlation was observed between thyroid area, weight and age of the subject. The normal range of thyroid uptake is in the range between (0.77% - 3.8%) and the thyroid area is in the range of (12.7 cm^2 to30.1 cm^2) there was a direct relationship between thyroid uptake and the thyroid area that when the area increase the uptake increase that shown in the following equation: $y= 0.054x + 0.89$ where x refers to thyroid area and y refers to uptake in percent. The result also shown that when thyroid weight increase the uptake increase as shown in the following equation: $y= 0.056x + 1.53$ where x refers to thyroid weight and y refers to uptake in percent. And the result shown that when BMI increase the uptake decrease as shown in the following equation: $y = - 0.033x + 2.82$ where x refers to BMI and y refers to uptake in percent. Finally the result also shown that when patient age increase the thyroid uptake decrease as shown in the following equation: $y = - 0.6x + 1.85$ where x refers to patient age and y refers to uptake in percent.

Chapter Three

Materials and Methods

Chapter Three

Materials and Methods

3.1 Materials

3.1.1 Design of the study

This is a cross-sectional study of a descriptive type where the data collected prospectively.

3.1.2 Population of the study

Sudanese male and female patients from all ages with hyperthyroidism diseases who are using antithyroid medication (Carbimazole) who are following up in RICK. The sample of this study were consisted of 51 patients with different hyperthyroid diseases referred to RICK from different hospitals and private clinics in Sudan. The sample includes different tribes and ethnic groups because RICK is the biggest central hospital in Sudan. All the investigations were done in radiation and isotopes center of Khartoum (RICK) including T.F.T and thyroid uptake in the period from December 2018 to December 2019.

3.1.2.1 Included criteria

Hyperthyroidism patients who are regularly using carbimazole for one month and above.

3.1.2.2 Excluded criteria

Patients with normal thyroid or hypothyroidism diseases.

Hyperthyroidism Patients who are not regular in using carbimazole.

3.1.3 Sample size and type

The sample of this study were consisted of 51 patients (40 female and 11 male) their age ranged from 23 to 67 years old with hyperthyroid referred to RICK from different hospitals and private clinics in Sudan. The sample includes different tribes and ethnic groups.

3.1.4 Place and duration of the study

The study been conducted at Khartoum Oncology Hospital (RICK) in Sudan, between (Dec2018-Dec2019).

3.2 Ethical approval

The study has been approved by college research board and participant were verbally agreed to participate in the study.

3.3 Method

3.3.1 Thyroid Function Test (TFT)

Thyroid function tests are blood tests used to evaluate how effectively the thyroid gland is working . The thyroid gland function depend on the presence of iodine content Is the most popular test .Because thyroid is the only organ in the body that takes up and uses iodine These tests include the thyroid-stimulating hormone test (TSH), the thyroxine test (T4), the triiodothyronine test (T3), the thyroxine-binding globulin test (TBG), the triiodothyronine resin uptake test (T3RU), and the longacting thyroid stimulator test (LATS).

3.3.2 Thyroid uptake scan

3.3.2.1 Gamma camera

The material used to collect the data was dual head SPECT, manufactured by MEDISO Company Hungary at 2005. Collimator used low energy general purpose (LEGP), window: 20% and the radiopharmaceutical used the Tc-99m injected intravenously, dose: 5mci (185Mbq) (+,- depending on extremes of body weight). Gamma camera consist of NAI crystal optically coupled to array of photomultiplier tube (head) & gantry is responsible of acquisition & storage of acquired images.

Figure 3.1: Dual head SPECT

gamma photon comes from radiopharmaceuticals injected to the patient , when it reaches the crystal it scintillate , this gamma photon is then converted to light photon then the photomultiplier tubes (PMT's) con dry it to electric signal & amplify it . The computer reconstruct & display two-dimential image on monitor.

3.3.2.2 Dose calibrator:

Ionization chamber constructed to measure the number of ions within the medium. It's usually consist of gas filled enclosure between two conducting electrodes, when gas is ionized by radioactive emission. The ions & diassociated electrons move to the electrode with opposite polarity creating an ionization current that can be measured

Ionization chamber are used to determine the exact activity of radioactive dose administered to patient.

Figure 3.2: Dose calibrator

3.3.2.3 Radiopharmaceutical used

Thyroid gland function and structure can be evaluated using uptake and Scintigraphy studies.

Technetium-99m, in the chemical form of pertechnetate (99m TcO4-), is also used for thyroid Scintigraphy and uptake the similarity of volume and charge between the iodide and pertechnetate ions is the explanation for the uptake of 99m Tc-pertechnetate by the thyroid gland. 99mTc-pertechnetate has been used worldwide to study the thyroid function because of a number of advantage, such as a short half-life (6 hours), short retention in the gland, and no ß- radiation, thus providing low dosimetry to the thyroid gland (10,000 times less than that of ^{131}I-iodide) , as well as to the body as a whole. Its gamma photon of 140 kev is ideal for imaging using scintillation cameras and in addition it has low cost and is readily available.

There is an international consensus that the radiopharmaceuticals of choice for thyroid gland imaging are 99m Tc-pertechnetate or ^{123}I-iodide. Although the thyroid does not organify 99mTc- pertechnetate, in the majority of cases the uptake and imaging data provide all the information needed for accurate diagnosis.

In rare instances, ^{123}I-iodide can subsequently be used for assessment of organification defects.

Despite these recommendations, most nuclear medicine laboratories in Brazil choose the radiopharmaceutical ^{131}I-iodide to study the thyroid gland. This practice can in part be explained by the fact that there is a lack of standard values for 99mTc- pertechnetate uptake by the thyroid gland. This study had the aim of standardizing a simple and fast method for performing thyroid uptake and Scintigraphy and defining the 99mTc-pertechnetate uptake values in normal individual (IAEA, 1995).

3.3.3 Method of data collection

3.3.3.1 Technique and methods of TFT

3.3.3.1.1 Patient preparations:

No preparation is necessary for a standard TFT test.

The procedure is quick, straightforward, and relatively painless. People may feel a slight pinch when the needle first enters the skin. There may also be some minor bleeding following the removal of the needle. Side effects are uncommon. When they do occur, they are usually mild and may include dizziness or nausea and slight skin bruising for a couple of days after the procedure.

A healthcare professional will usually draw blood from a vein on the inside of the elbow. They will begin by cleaning the skin and may then place an elastic band around the upper arm to make the vein easier to access. They will insert a needle into the vein, allowing blood to flow into the connecting tube and vial. Once the vial contains enough blood to carry out the test, the healthcare professional will remove the needle and elastic band and place cotton wool or a bandage over the puncture site. After labeling the blood sample, they will send it to a laboratory for testing.

3.3.3.1.2 Technique of measuring TFT

3.3.3.1.2.1 Clinical Utility of TT4 and TT3 Measurements

The diagnostic accuracy of total hormone measurements would be equivalent to that of free hormone tests if all patients had similar binding protein concentrations. In fact, a recent study has reported that a screening cord blood TT4 < 7.6 µg/dL (< 98 nmol/L) can be used as a screening test for congenital hypothyroidism. Unfortunately, many conditions are associated with TBG abnormalities that distort the relationship between total and free thyroid hormones. Additionally, some patients have abnormal thyroid hormone binding albumins (dysalbuminemias), thyroid hormone autoantibodies, or are taking drugs that render total hormone measurements diagnostically unreliable. Consequently, TT4 and TT3 measurements are rarely used as stand-alone tests, but are typically employed in conjunction with a direct TBG measurement or an estimate of binding proteins [i.e. a thyroid hormone binding ratio test, THBR, that can be used to calculate a free hormone index (FT4I or FT3I). This index approach effectively corrects for the most common thyroid hormone binding protein abnormalities that distort total hormone measurements. Because free hormone immunoassays are more technically challenging than total hormone measurements total hormone tests can useful confirmatory when a free hormone immunoassay result appears questionable, especially in pregnancy and critical illness where changes in binding protein concentrations and affinity for thyroid hormones can occur. (Spencer, Carole et. al., 2013).

3.3.3.1.2.2 TT4 and TT3 Reference Ranges

Total T4 reference ranges have approximated 55 - 177 nmol/L for more than four decades, although some between-method differences and sample-related variability remains. The IFCC C-STFT found that most TT4 methods report values within 10 percent of the ID-LC-MS/MS RMP.

TT3 reference ranges generally approximate 1.0 – 3.3 nmol/L. However, TT3 methods display far more between-method variability than TT4, and most display more than a 10 percent bias relative to the reference method. (Spencer, Carole et. al., 2013).

3.3.3.1.2.3 Clinical Utility of TSH Measurements

In the outpatient setting the reliability of TSH testing is not influenced by the time of day of the blood draw, because the diurnal TSH peak occurs between midnight and 0400 [583-586]. Third-generation TSH assays (FS ~0.01 mIU/L) have now become the standard of care because they can reliably detect the full spectrum of thyroid dysfunction from overt hyperthyroidism to overt hypothyroidism, provided that hypothalamic-pituitary function is intact and thyroid status is stable.

3.3.3.1.2.4 TSH Reference Range

The complex log/linear TSH/FT4 relationship dictates that TSH will be the first abnormality to appear with the development of mild (subclinical) hypo- or hyperthyroidism. It follows that the setting of the TSH reference limits critically influences the frequency of diagnosing subclinical thyroid disease.

Guidelines recommend that "TSH reference intervals should be established from the 95 percent confidence limits of the log-transformed values of at least 120 rigorously screened normal euthyroid volunteers who have: (a) no detectable thyroid autoantibodies, TPOAb or TgAb (measured by sensitive immunoassay); (b) no personal or family history of thyroid dysfunction; (c) no visible or palpable goiter and, (c) who are taking no medications except estrogen" . (Spencer, Carole et. al., 2013).

3.3.3.2 Technique and methods of thyroid uptake

3.3.3.2.1 Patient preparations

The patient was prepared according to the following points: patient should stop thyroid media, patient also should stop taking any food contain iodine. If the patient is female, will be inspected if she is pregnancy, the patient will return to their physicians. In case of breast feeding, the patient will be asked to stop feeding for a while until the radioactive substance been execrated from the body. The history of the patient should be taking into account, and the clinical condition should be noted. The related study must be available, which is help full in diagnosis.

3.3.3.2.2 Technique of uptake

Before the injection of the radioactive dose, it must be measure accurately in the dose calibrator, and take a 60 seconds image of the full syringe in the gamma camera. Then inject the dose of 5.0 mci of 99mTcO4 – for adult patient. The dose can be minimizing in case of children or low weight patient using different calculation methods. (it is also can be used to maximize the dose in case of high weight patients). After the injection, 60 seconds image for the empty syringe was taken.The patient waits for 15 minutes, for maximum concentration of sodium pertecnetate. Firstly 330 K. counts image AP was taken in supine position with pillow under the shoulder and chin hyper extended for good visualizations of thyroid gland; this image is used in calculation of thyroid uptake.

If there an enlarged in the thyroid gland marker with point source 99mTc or 57Co will be used in the supra-sternal notch (S.S.N) to determine the extension of the gland.

If there is suspicious of any disorder in the first image, additional images (RAO, LAO) will be done, or by using the marker in the location of abnormality.

Lastly ROI was drawn around full syringe, empty syringe and AP patient image, the computer program will automatically measure the actual activity injected to the patient by subtract the empty activity from the full, after that it can measure the thyroid uptake using special nuclear medicine program.

The method for the calculation of thyroid uptake, based on images of the gland and syringe counts before and after radiopharmaceutical injection, was previously described by simplified for routine use. The number of counts present in the thyroid

(T) was determined by an automatic region of interest (ROI) draw around the borders of the gland. Another ROI was drawn by the same process just below the gland for background subtraction (BG). The counts in the syringe before and after radiopharmaceutical injection were obtained directly from the images. All counts were corrected for the acquisition time and decay of technetium-9m. the thyroid uptake (TU) was calculated automatically by subtraction before & after injection of the radioactive isotopes & background of surround tissues according to the software of the machine in a form of percentage. Berman, M (1988).

3.3.3.3 Variable of data collection

The data in in this study were collected using the following variable: Age, gender, height, weight, carbimazole dose, carbimazole used period, TFT result while using medication, TFT result after stopping medication, medication discontinued period, and thyroid uptake.

Name	Sex	Age	Weight	Height	Medication		First TFT			Second TFT			Thyroid uptake	Delay period
					Dose	**Period**	**T3**	**T4**	**TSH**	**T3**	**T4**	**TSH**		

Table 3.1: Simple Example of Master Data Sheet

3.3.3.4 Method of data analysis

Data was analyzed by using Excel Microsoft Program, SPSS vision 21.0 under windows and Qlik view program.

Chapter Four

Result

Chapter Four

Result

Table 4.1 The average values for body characteristics and TFT levels

Variables	3 days delay	5 days delay	7 days delay
Age	37.29	47.82	47.71
Weight	62.24	65.24	64.18
Height	164	164.29	164.29
Dose	27.65	25.29	27.65
Period	4.06	6.59	5
T3	5.2	5.28	5.34
T4	225.59	231.86	246.19
TSH	0.17	0.13	0.06
T3	6.33	9.18	9.96
T4	246.38	318.55	381.72
TSH	0.03	0.05	0.04
Thyroid uptake	21.35	18.82	23.31

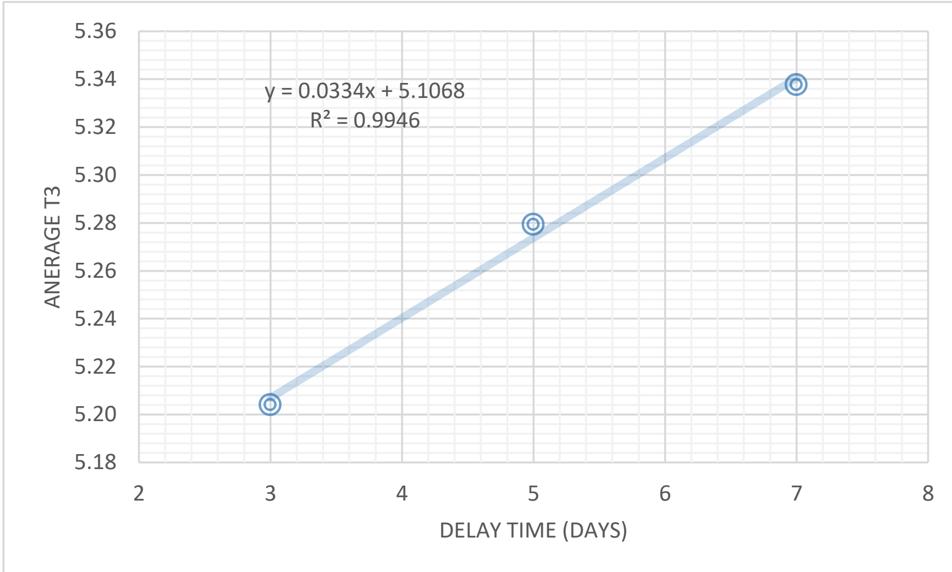


Figure 4.1 scatter plot show a direct linear association of average T3 level with delay time.

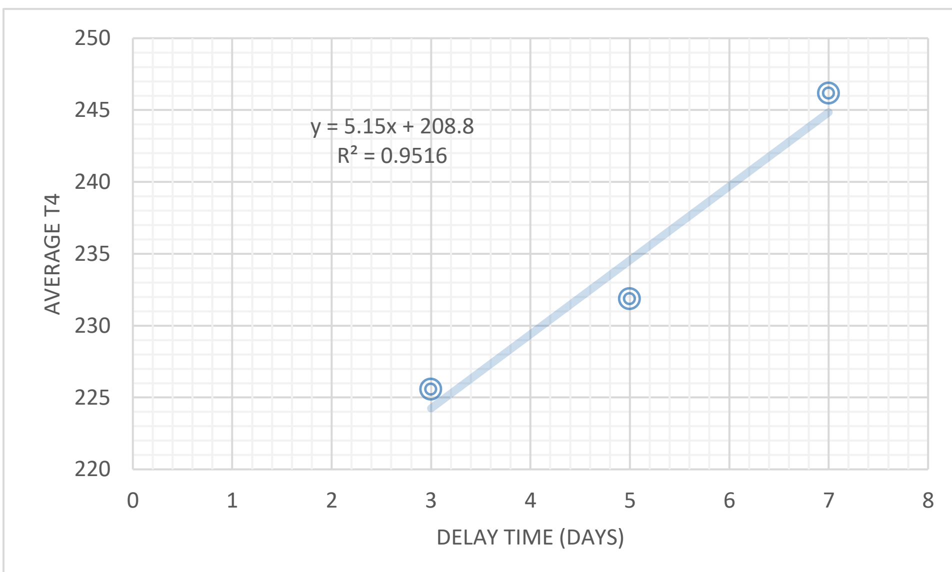


Figure 4.2 scatter plot show a direct linear association of average T4 level with delay time.

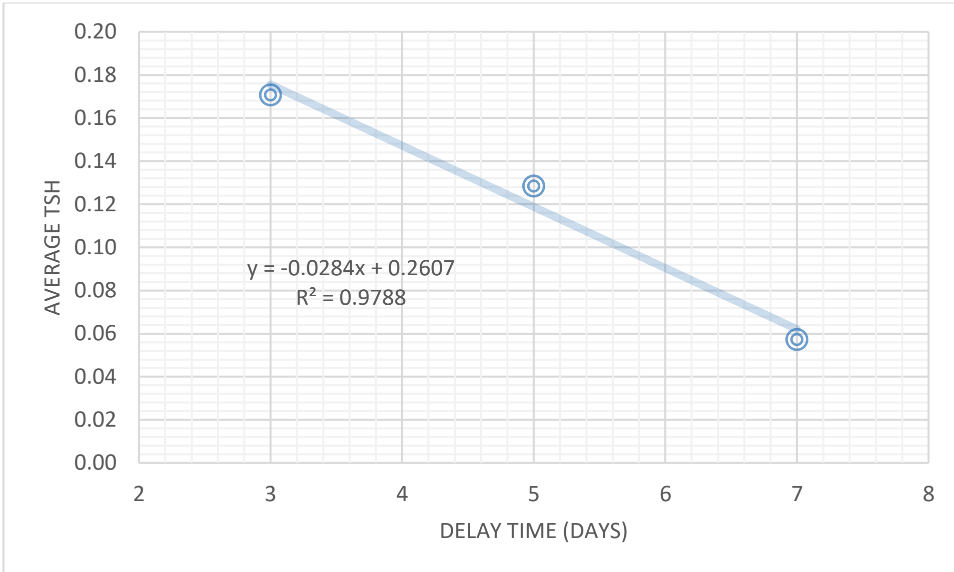


Figure 4.3 scatter plot show a direct linear association of average TSH level with delay time.

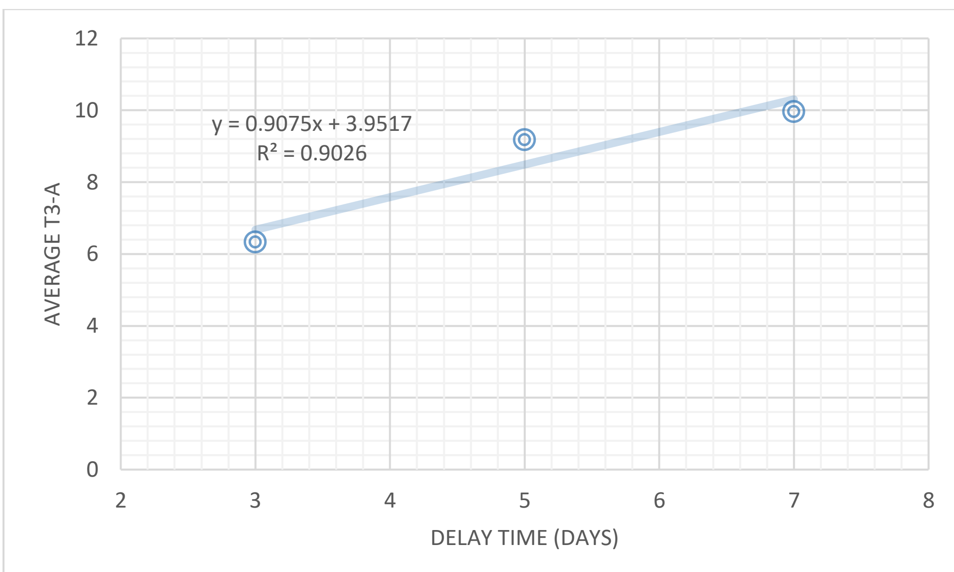


Figure 4.4 scatter plot show a direct linear association of average T3-A level with delay time.

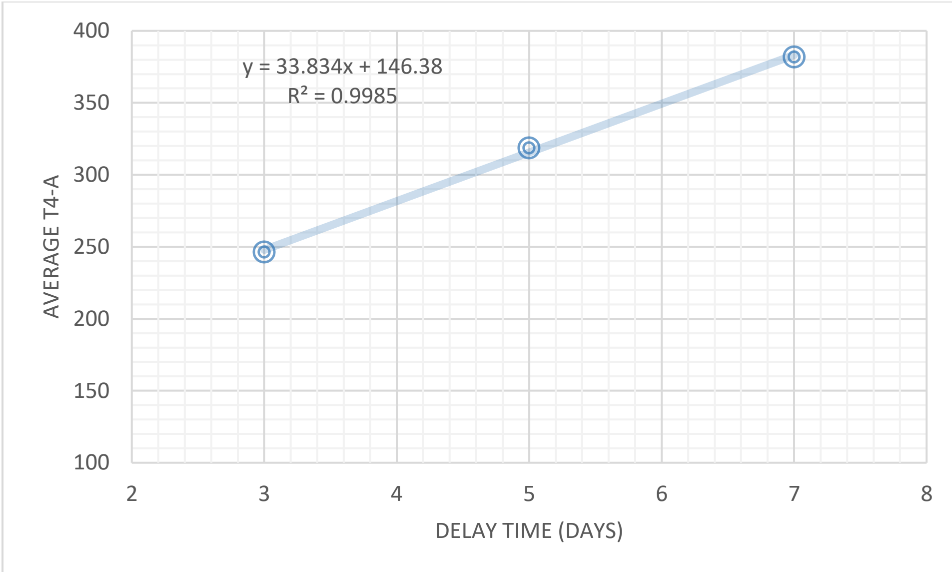


Figure 4.5 scatter plot show a direct linear association of average T4-A level with delay time.

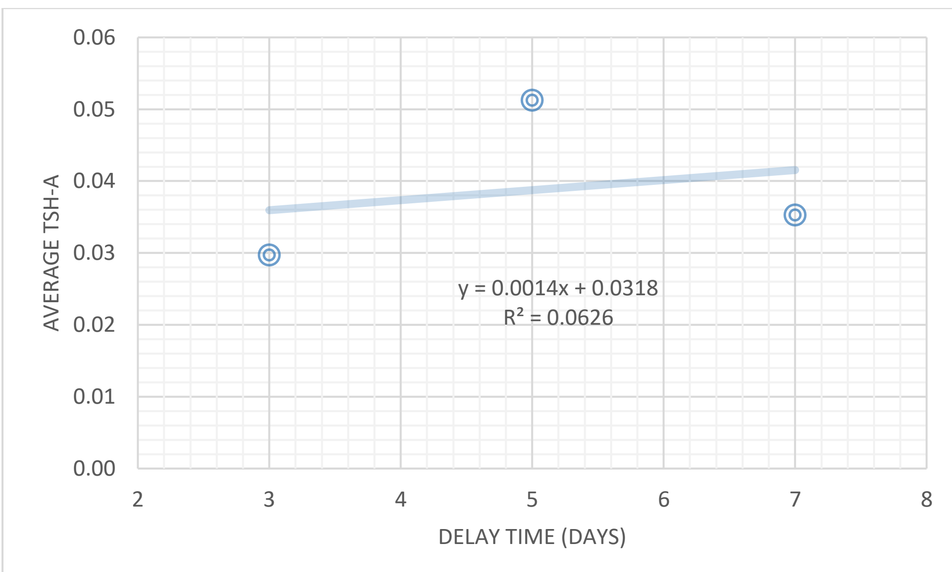
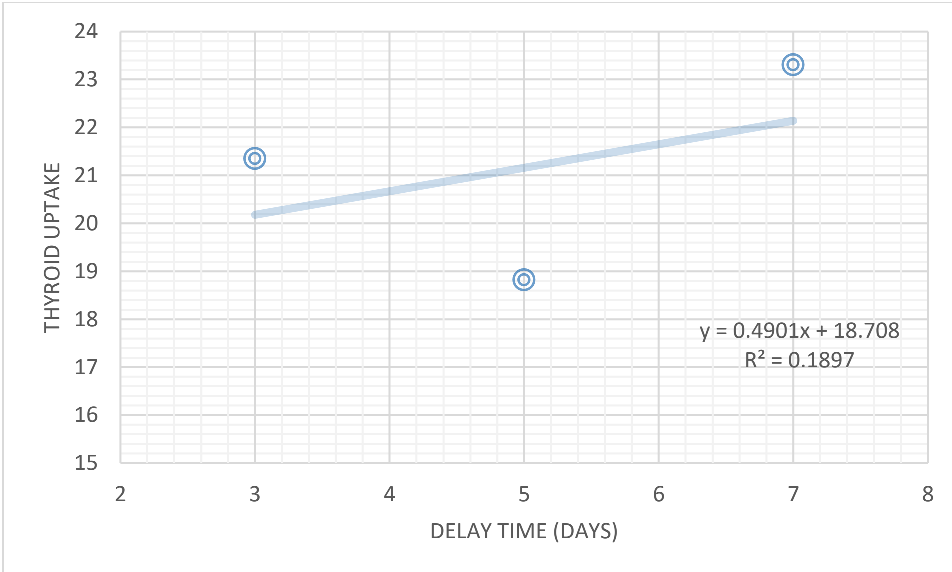


Figure 4.6 scatter plot shows the relation between TSH-A level average with delay time.



m **Figure 4.7** scatter plot shows the relation between thyroid uptake average with delay time.

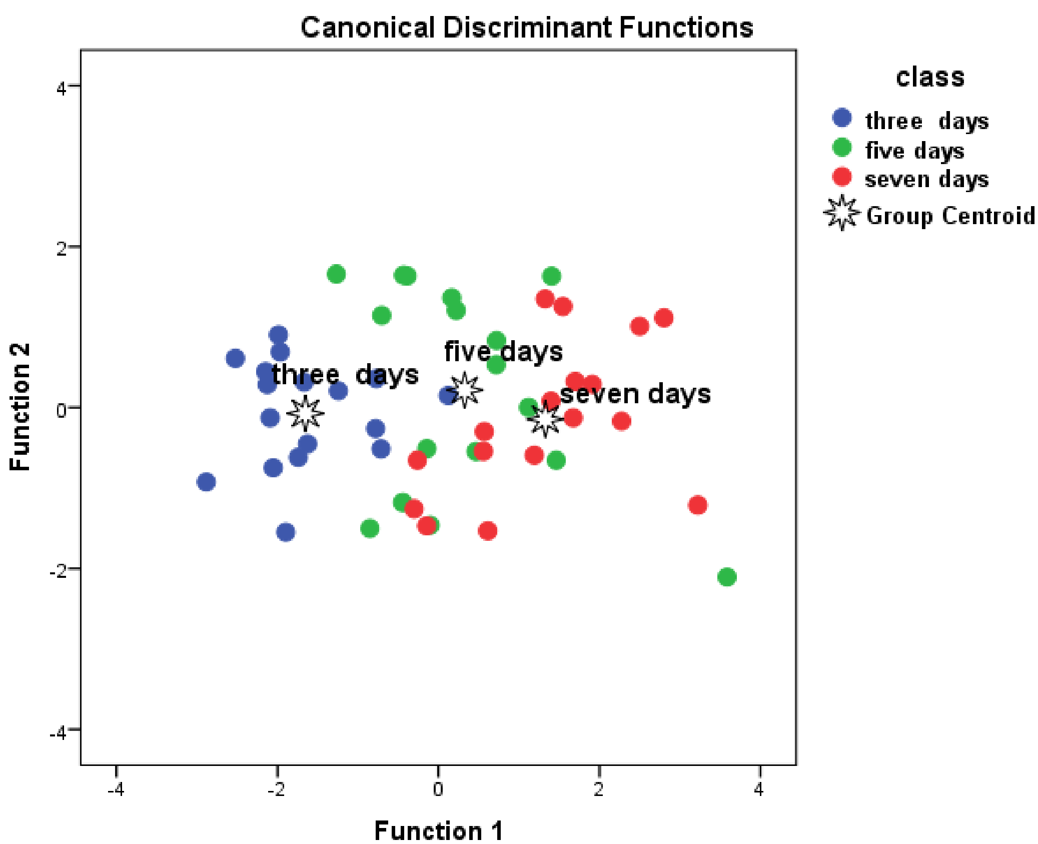


Figure 4.8 Scatter of the patients groups as a results of delay time using T4 and age as input values for linear discriminant analysis function

Classification Results						
Cass			Predicted Group Membership			Total
			three days	five days	seven days	
Original	Count	three days	16	1	0	17
		five days	2	11	4	17
		seven days	0	5	12	17
	%	three days	94.1	5.9	0	100
		five days	11.8	64.7	23.5	100
		seven days	0	29.4	70.6	100
76.5% of original grouped cases correctly classified.						

Table 4.2 crosstabulation matrix of the delay dates as classes classified by linear discriminant analysis using T4 and age as input values

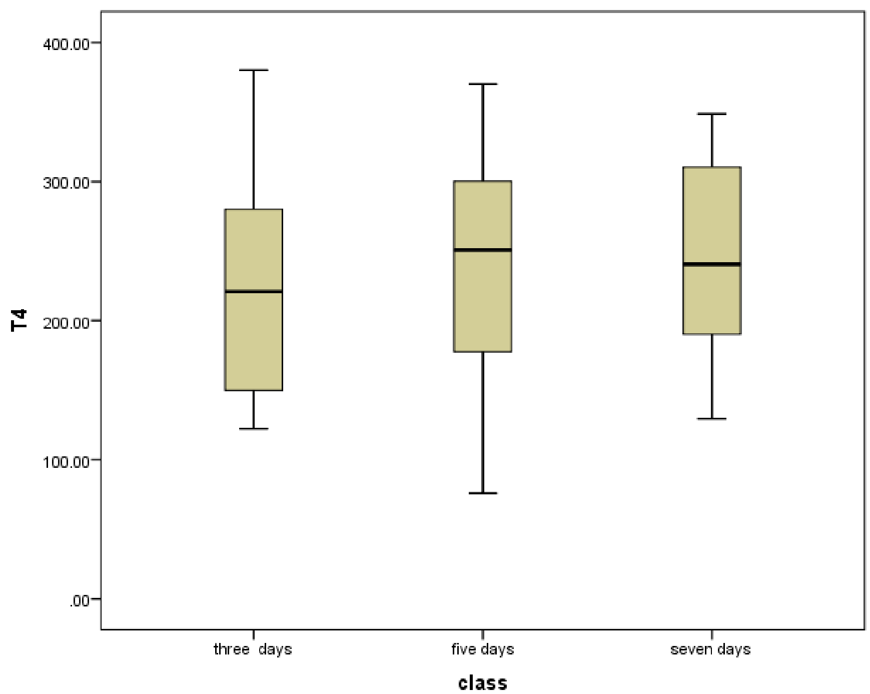


Figure 4.9 error bar plot of T4 average values for the delay dates.

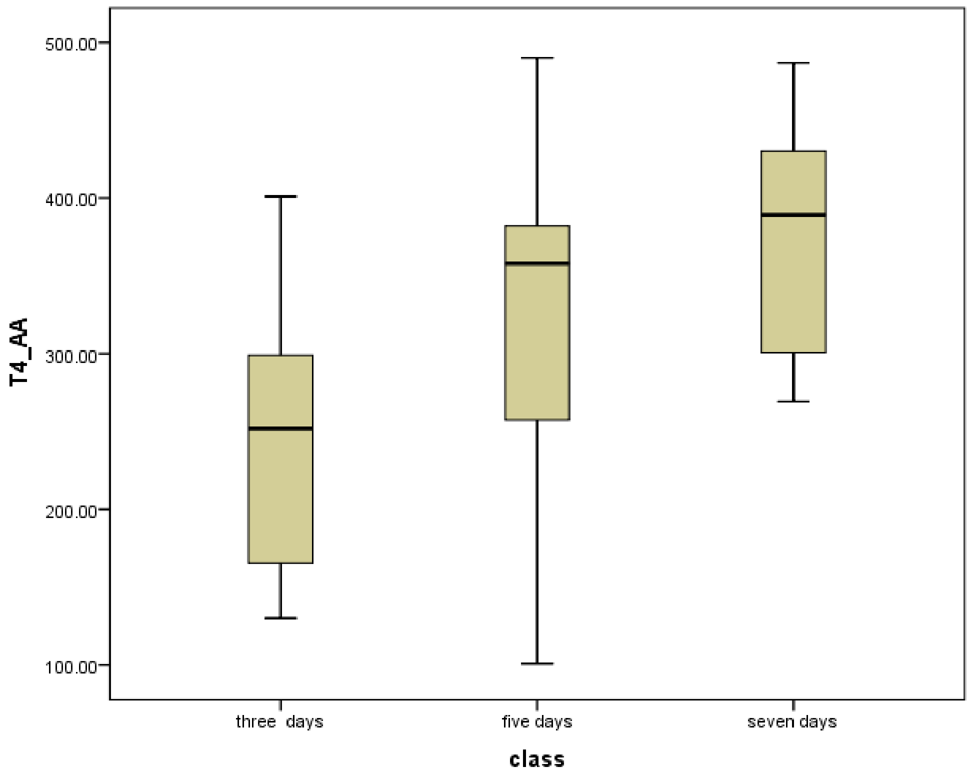


Figure 4.10 error bar plot of T4_AA average values for the delay dates.

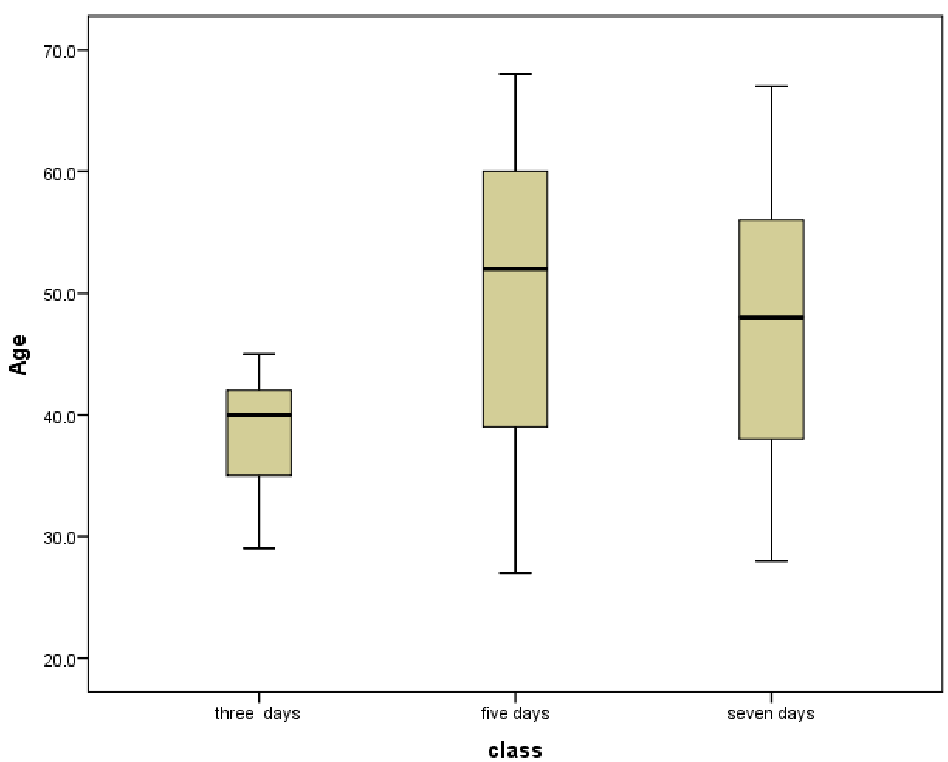


Figure 4.11 error bar plot of patients Age average values with the delay dates.

Chapter Five

Discussion, Conclusion and Recommendation

Chapter Five

Discussion, Conclusion and Recommendation

5.1 Discussion.

The data of this study collected from 51 hyperthyroid patients (from both genders and different ages, MBI, medication doses and period of using medication) who were using Carbimazole. Initially a TFT has been collected from all patients while they were using Carbimazole. These patients were divided according to the first TFT results into three groups; each group had a different delay period of Carbimazole for thyroid uptake scan. After delay period, a second TFT was collected from all patients to check hormones status:

- Group A had stopped Carbimazole for 3 days. This group had an average age of 37 years, average weight of 62.24 kg, the average height was 164 cm, the average Carbimazole dose had been taken is 27.65 and the average period Carbimazole had been taken was 4 months. Their first TFT average results were (T3: 5.2 nmol/l, T4: 225.59 nmol/l and TSH: 0.17 mU/l).

  Thyroid uptake average was 21.35% and the second TFT result average was: (T3: 6.33 nmol/l, T4: 246.38 nmol/l and TSH: 0.03 mU/l).
- Group B had stopped Carbimazole for 5 days. This group had an average age of 47 years, average weight of 65.24 kg, the average height was 164 cm, the average Carbimazole dose had been taken was 25.29 and the average period Carbimazole was taken is 6 months and a half. Their first TFT average results were (T3: 5.28 nmol/l, T4: 231.86 nmol/l and TSH: 0.13 mU/l).

  Thyroid uptake average was 18.82% and the second TFT result average was: (T3: 9.18 nmol/l, T4: 318.55 nmol/l and TSH: 0.05 mU/l).

- Group C had stopped Carbimazole for 7 days. This group had an average age of 47 years, average weight of 64.18 kg, the average height was 164.29 cm, the average Carbimazole dose had been taken is 27.65 and the average period Carbimazole had been taken was 5 months. Their first TFT average results were: (T3: 5.34 nmol/l, T4: 246.19 nmol/l and TSH: 0.06 mU/l).
  Thyroid uptake average was 23.31% and the second TFT result average was: (T3: 9.96 nmol/l, T4: 381.72 nmol/l and TSH: 0.04 mU/l).

The results showed that there is a direct linear association between T3 level and the delay period; as the delay period increase the T3 level increases as shown in Figure 4.4.

There was also a direct linear association between T4 level and the delay period; as the delay period increase the T4 level increases as shown in Figure 4.5.

The results showed that the TSH level decrease as the delay period increases as shown in Figure 4.6.

After comparing thyroid uptake average from all the groups, the result showed that thyroid uptake was not affected by the delay period as shown in Figure 4.7.

5.2 Conclusion.

The main objective of this study was to study the ideal delay period of carbimazole for hyperthyroidism patients using thyroid function test.

A number of thyroid uptake scans and TFT were conducted to estimate the ideal delay period of Carbimazole that can save patients from severe elevation of thyroid hormones and TSH level and serve thyroid uptake scan by ultimate advantage with the least risk on patients.

The results showed that thyroid uptake do not change by the increase of the delay time.

In the other hand, as the delay period increased, thyroid hormones increased and TSH decreased leading to a severe elevation of hormones that may lead to thyroid storm.

In summary, this study showed that thyroid uptake scan can be done after a delay period of 3 days and still have the same thyroid uptake as 5 or 7 days but with the least risks on patients.

5.3 Recommendation.

- 3 days off Carbimazole should be submitted as the ideal delay period for thyroid uptake scan.
- Thyroid uptake scan can be used as a first diagnosis or after one year of using Carbimazole. Follow-up of hyperthyroidism can be done effectively by only TFT.
- Further studies can be made on wither thyroid uptake scan can be achieved properly while the patient is on Carbimazole.

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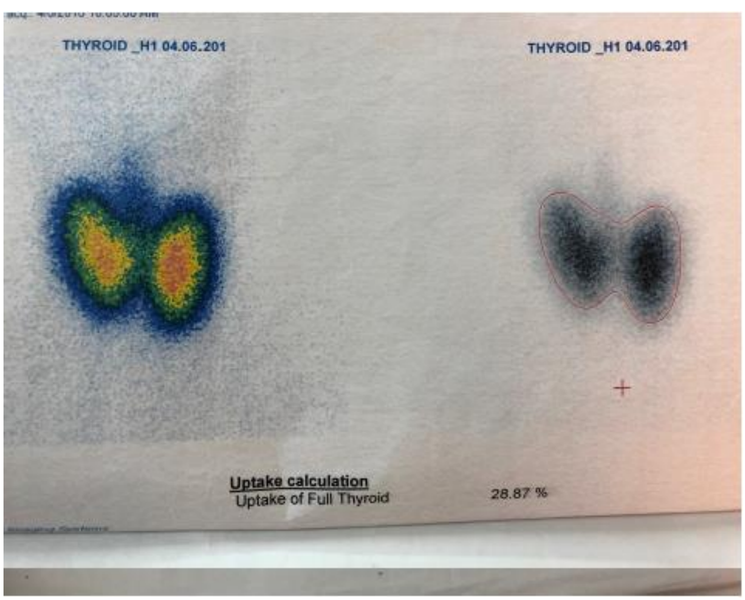
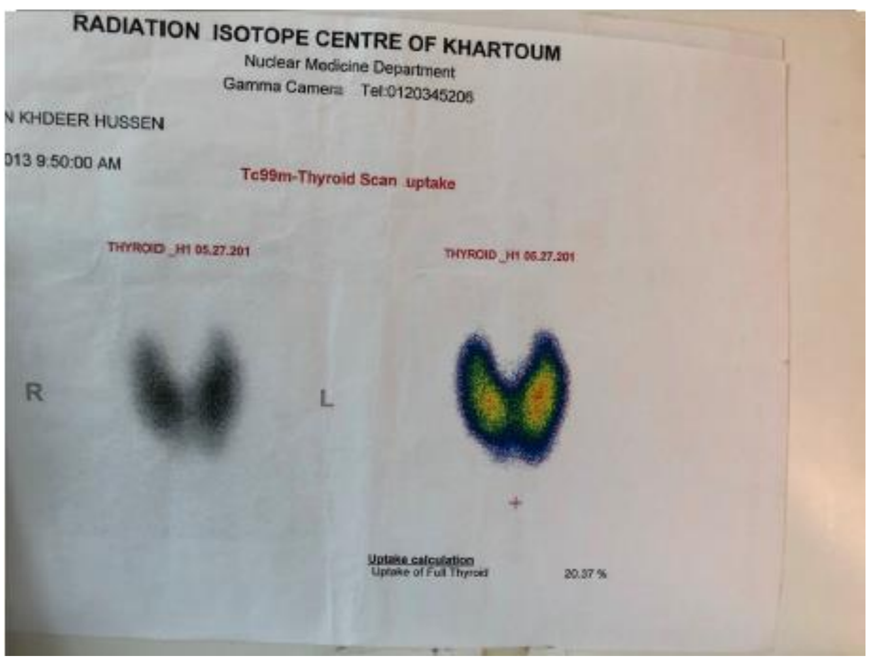
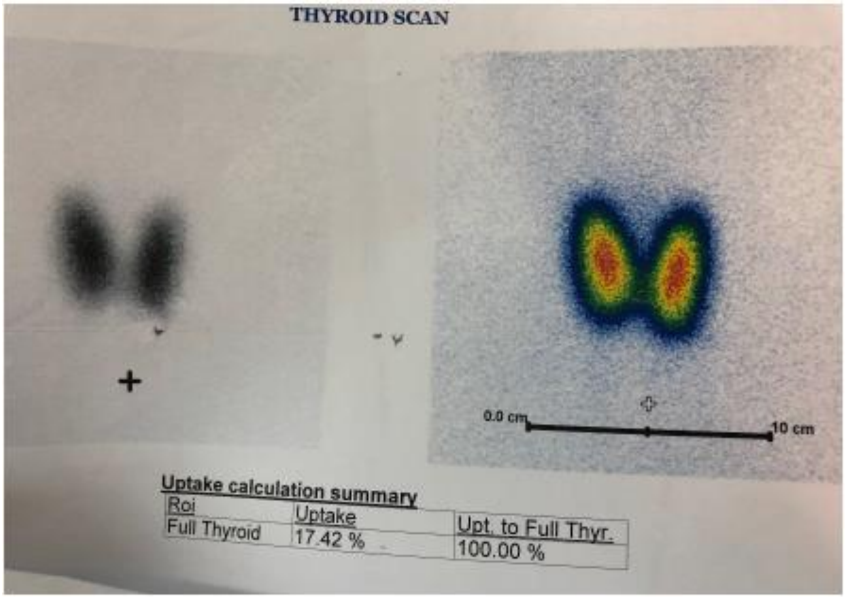
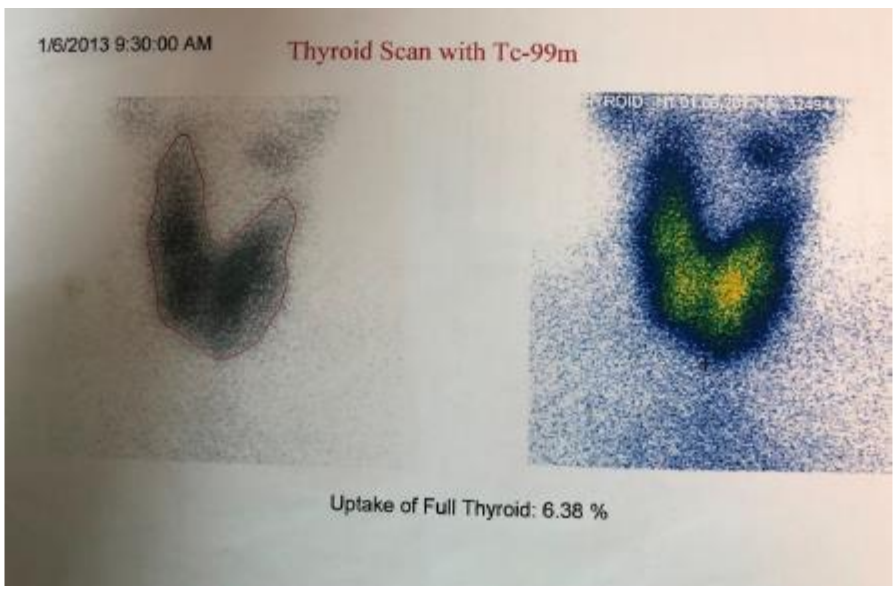
Appendix

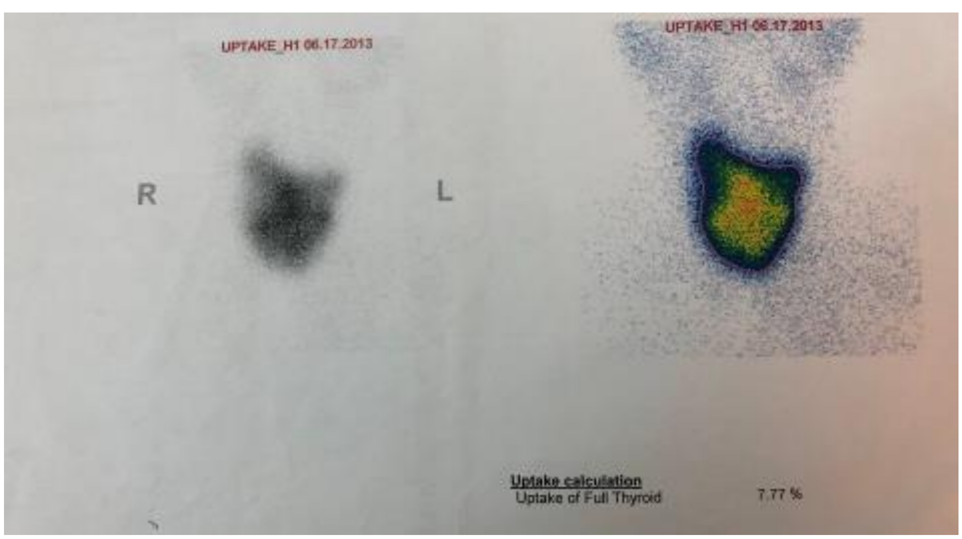
Sex	Age	Weight	Height	Medication		First TFT			Second TFT			Thyroid uptake	Delay period
				Dose	Period	T3	T4	TSH	T3	T4	TSH		
F	35	60	163	30	3 month	2.45	220.8	1.8	5.68	227.8	0.005	4.3	3 days
F	43	52	169	25	8 month	2.76	144.1	0.005	1.53	151.8	0.01	25.7	3 days
F	38	65	157	30	7 month	2.90	150	0.1	6.29	164.7	0.05	7.04	3 days
F	30	66	157	15	4 month	2.4	261	0.01	6.3	360	0.01	23.34	5 days
F	42	52	160	30	12 month	2.5	225	0.001	5.7	393	0.16	12.90	5 days
M	45	77	173	15	1 month	2.91	75.9	0.49	8.35	257.4	0.01	17.42	5 days
F	34	60	167	20	1 month	2.49	140.9	0.003	4.90	269.3	0.006	29.6	7 days
M	45	77	180	30	5 month	2.67	330.2	0.03	7.98	411.8	0.039	11.4	7 days
F	67	65	158	40	24 month	2.99	240.6	0.01	7.2	389.1	0.01	24.7	7 days

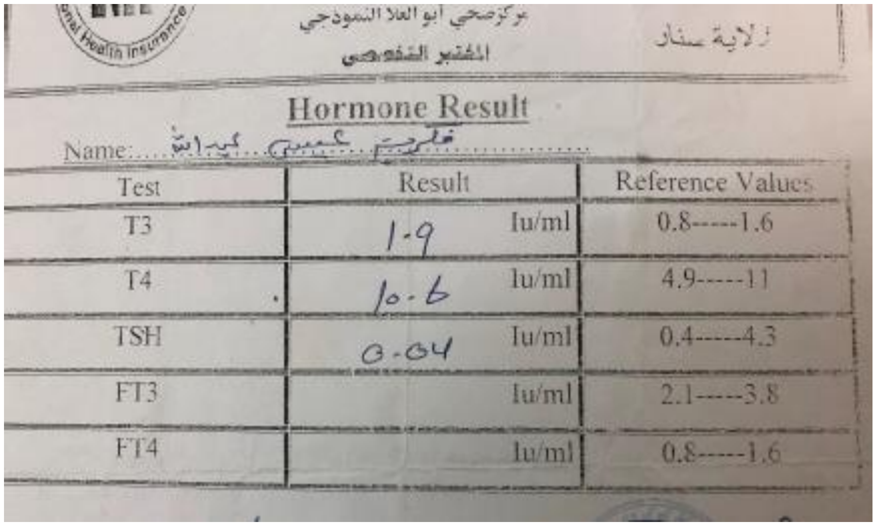





THYROID SCAN
0.0 cm
10 cm
Uptake calculation summary
Roi
Uptake
Upt. to Full Thyr.
Full Thyroid
17.42 %
100.00 %


1/6/2013 9:30:00 AM
Thyroid Scan with Tc-99m
Uptake of Full Thyroid: 6.38 %


UPTAKE_H1 06.17.2013
R
L
UPTAKE_H1 06.17.2013
Uptake calculation
Uptake of Full Thyroid
7.77 %

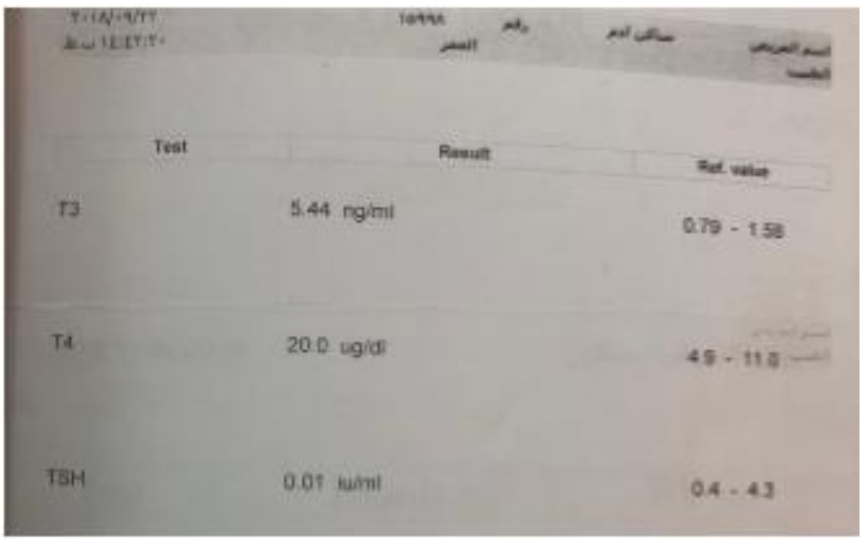


مركز صحي أبو العلا النموذجي
المختبر

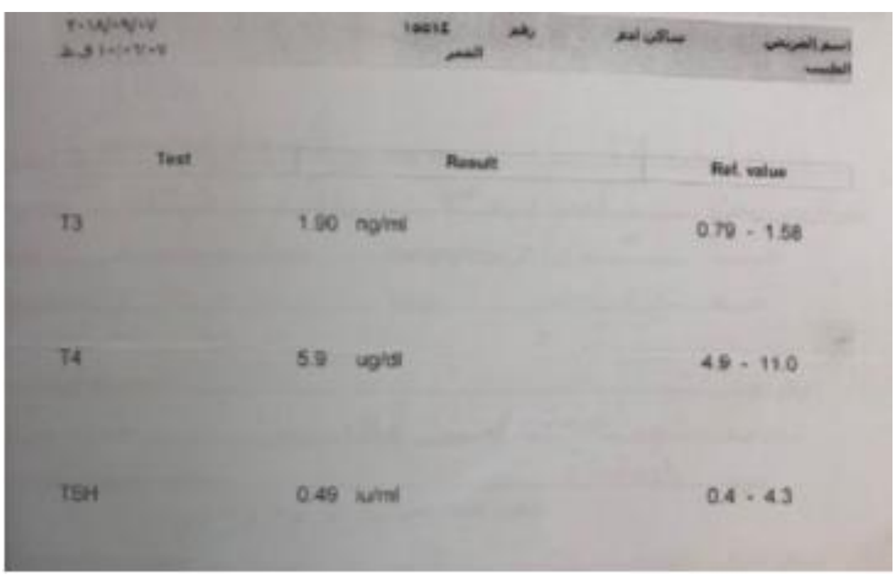
Hormone Result

Name: ...

Test	Result		Reference Values
T3	1.9	Iu/ml	0.8-----1.6
T4	10.6	Iu/ml	4.9-----11
TSH	0.04	Iu/ml	0.4-----4.3
FT3		Iu/ml	2.1-----3.8
FT4		Iu/ml	0.8-----1.6



Test	Result	Ref. value
T3	5.44 ng/ml	0.79 - 1.58
T4	20.0 ug/dl	4.9 - 11.0
TSH	0.01 iu/ml	0.4 - 4.3



Test	Result	Ref. value
T3	1.90 ng/ml	0.79 - 1.58
T4	5.9 ug/dl	4.9 - 11.0
TSH	0.49 iu/ml	0.4 - 4.3