بسم الله الرحمن الرحيم

Sudan University of Science and Technology

College of Graduate Studies

Assessment of Serum Total Cholesterol Level of Sudanese patients
with Thyroid Dysfunction in Khartoum State

**تقييم مستويات الكوليسترول الكلي لدي المرضي السودانيين المصابين بنشاط
و خمول الغدة الدرقية في ولاية الخرطوم**

A dissertation Submitted in Partial Fulfilment for M.Sc Degree
in Clinical Chemistry

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قال تعالى:

بسم الله الرحمن الرحيم

{.. إنما يخشي الله من عباده العلماء..}

صدق الله العظيم

(سورة فاطر)

Dedication

TO................

MY Father.................Who Work hardly for us.

TO....................

MY Mother.......................Who taught me

How I could be human

MY beloved brother and sisters

TO....................

The people, whom I love, respect and appreciate.

ACKNOLEDGMEN

Abstract:

This study was carried out during the period of (February – July 2014) in order to assess the level of total serum cholesterol in 100 patients with hyperthyroidism and hypothyroidism. Three groups were involved in this study. 50 patients with hypothyroidism and 50 with hyperthyroidism and 30 subjects apparently healthy as control group. All the participants attended at Khartoum Teaching Hospital.

Five ml of venous blood was collected from patients, Serum was used to measure T3, T4, TSH and total cholesterol then the data was analyzed by using the computer program SPSS version 11.5 to obtain Mean $\pm$ SD, Independent T test and correlations. Level of significance was ≤ 0.05.

The automated Immunoassay method was used for estimation of thyroid function tests (TFT). The enzymatic colorimetric (Oxidase/Peroxidase) method was used for estimation of total cholesterol levels.

The study findings showed that majority of patients were females and the patients representing the age between 30 -45 years.

The results showed that the level of total cholesterol was significantly decreased in patients with hyperthyroidism compared to control subjects. (128 mg/dl $\pm$ 30 mg/dl) versus (175 mg/dl$\pm$ 27 mg/dl) respectively, (P value < 0.05). The level of total cholesterol was significantly increased in patients with hypothyroidism compared to control subjects (198 mg/dl $\pm$ 43 mg/dl) versus (175 mg/dl $\pm$ 27mg/dl) respectively, (P value < 0.05).

There was a significant positive correlation between the level of serum total cholesterol and levels of TSH (r=0.48, P value= 0.000), the results also showed there a significant negative correlation between levels of serum total cholesterol and levels thyroid hormones (T3 and T4), (r=-0.57, P value =0.000) and(r= -0.59, P value= 0.000).

The results concluded that hyperthyroidism and hypothyroidisms have an effect on total cholesterol levels resulting dyslipidemia.

الخلاصة

أجريت هذه الدراسة خلال الفترة (فبراير - يوليو) 2014 في أجل تقييم مستوى الكوليسترول في المصل من المرضى الذين يعانون من زيادة نشاط او خمول الغدة الدرقية. وشاركت ثلاث مجموعات في هذه الدراسة. 50 من المرضى الذين يعانون قصور الغدة الدرقية و50 من المرضي يعانون من فرط نشاط الغدة الدرقية و50 اصحاء ظاهريا ليس لديهم أي تاريخ من اضطرابات الغدة الدرقية.جميع المشاركين في الدراسه هم من مستشفى الخرطوم التعليمي.

أظهرت نتائج الدراسة أن غالبية المرضى هم من الإناث وان الغالبية في سن 30 -45 عاما.

تم استخدام طريقة المقايسة المناعية الآلية لتقدير اختبارات وظائف الغدة الدرقية .

استخدمت الطريقة الأنزيمية لتقدير مستويات الكوليسترول الكلي.

واتضح من الدراسة ان في مرضي فرط نشاط الغده الدرقية ارتفاع مستويات T3 و T4 زيادة زات دلالة إحصائية مقارنة بالاصحاء، ولكن أظهرت القيم TSH خفض بالمقارنة مع الاصحاء.

واتضح من الدراسة ان في مرضي قصور نشاط الغدة الدرقية انخفاض مستويات T3 و T4 انخفاض ذو دلالة إحصائية مقارنة بالاصحا، ولكن هناك زيادة في مستويات TSH مقارنة بالاصحاء.

أظهر النتائج أن مستوي الكوليسترول الكلي انخفض ذو دلالة معنوية في المرضى الذين يعانون من فرط نشاط الغدة الدرقية بالمقارنة مع الاصحاء. (128   ± 30) مقابل (175 ± 27) على التوالي، (قيمة 0.05> P). بينما إرتفعت مستويات الكولسترول الكلي بشكل ملحوظ في المرضى الذين يعانون من قصور الغدة الدرقية عند المقارنة بالاصحاء(198 ± 43) مقابل (175 ± 27) على التوالي، (قيمة 0.05> P).

هناك علاقة إيجابية ذات دلالة إحصائية بين مستوى الكوليسترول الكلي في الدم ومستويات (r=0.48 TSH, p=0.000)، وأظهرت النتائج أيضا أن هناك علاقة سالبة ذات دلالة إحصائية بين مستويات الكولسترول الكلي في الدم ومستويات هرمونات الغدة الدرقية (T3 و T4) و(0.000 = P , r=-0.57) و(0.000 = P , r=-0.59).

أظهرت هذه الدراسة أن خمول و نشاط الغدة الدرقية لهما تأثير على مستويات الكوليسترول الكلي مما أدى اضطراب شحميات الدم.

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Abbreviations

ACTH	AdenoCortico Tropic Hormone
AMP	Adenosine Mono phosphate
ATP	Adenosine Tri phosphate
D2	Deiodinase type 2
DIT	Diiodotyrosine
FT3	Free Triiodothyronine
FT4	Free Thyroxine
FSH	Follicle Stimulating Hormone
GH	Growth Hormone
HCG	Human chorionic gonadotropin
HDL	High Density Lipoprotein
HMG-COA	3-Hydroxy 3-Methylglutaryl COA
LH	Lutinizing Hormone
LDL	Low density Lipoprotein
LpL	Lipoprotein lipase
MIT	Monoiodotyrosine
NTI	Non Thyroidal illness
PRL	Prolactin
RCT	Reverse Cholesterol Transport

rT3	Reverse Triiodothyronine
rT4	Reverse Thyroxine
SCAP	ThyroPeroxidase Antibodies
SRE	Sterol Regulatory Element
SREBP	Sterol Regulatory Element-Binding Protein
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxin Binding Globulin
THBR	Thyroid Hormone Binding ratio
TPBA	Thyroxine Binding Pre albumin
TPO	ThyroPeroxidase Antibodies
TRH	Thyroid Releasing Hormone
TSH	Thyroid Stimulating Hormone
TSHR	Thyroid Stimulating Hormone Receptor
TSHR-TSI	Thyrotropin receptor antibodies
TT3	Total Triiodothyronine
TT4	Total Thyroxine
VLDL	Very Low Density Lipoprotein

CHAPTER ONE

Introduction and

Literature Review

1. Introduction and literature review

1.1 Introduction:

Thyroid gland disorders are the most abundant endocrine disorder in the world second only to diabetes mellitus. (Heuck, 2000).Thyroid disorder is a general term representing several different diseases involving thyroid hormones and the thyroid gland. Thyroid disorders are commonly separated into two major categories, hyperthyroidism and hypothyroidism, depending on whether serum thyroid hormone levels (T4 and T3) are increased or decreased, respectively. The prevalence and incidence of thyroid disorders is influenced primarily by sex and age. Thyroid disorders are more common in women than men, and in older adults compared with younger age groups. (Sisk, 2005)

Thyroid hormones regulate a wide array of metabolic activities; thyroid hormones are important modulator of intermediary metabolism. They affect synthesis, mobilization and degradation of lipids, although degradation is influenced more than synthesis. Consequently, thyroid dysfunction particularly hypothyroidism is associated with dyslipidemia which increase the risk of endothelial dysfunction, hypertension and cardiovascular diseases. Thyroid hormones induce the 3-hydroxy-3-methylglutaryl- coenzyme A (HMG-CoA) reductase, which is the first step in cholesterol biosynthesis. Although decreased thyroid function is accompanied by reduced activity of HMG-CoA reductase, Total cholesterol (TC) and LDL-C levels are increased in patients with hypothyroidism. Moreover, a decrease in lipoprotein lipase activity is found in hypothyroidism, decreasing the clearance of Triglyceride and LDL. Moreover, decreased activity of the cholesterol ester transfer protein results in reduced transfer of cholesteryl esters from HDL to VLDL. (Santamarina-Fojo *et al.*, 2004)

In hyperthyroidism TC and LDL levels were decreased significant statistically. Despite the increased activity of HMG-CoA reductase, the cholesterol levels tend to be decreased in hyperthyroidism due to augmented excretion of cholesterol by bile together with enhanced receptor mediated catabolism of LDL particles. (Duntas, 2002)

According to previous study about the effect of thyroid hormone dysfunction on lipid metabolism this study was conducted to evaluate level of serum total cholesterol in both hyperthyroidism and hypothyroidism.

1.2 Literature Review

1.2.1 Endocrine System:

Is a collection of glands of an organism that secrete hormones directly into the circulatory system to be carried toward a distant target organ. The major endocrine glands include the pineal gland, pituitary gland, pancreas, ovaries, testes, thyroid gland, parathyroid gland, hypothalamus, gastrointestinal tract and adrenal glands. The endocrine system is in contrast to the exocrine system, which secretes its hormones using ducts. The endocrine system is an information signal system like the nervous system, yet its effects and mechanism are classifiably different. The endocrine system's effects are slow to initiate, and prolonged in their response, lasting from a few hours up to weeks. The nervous system sends information very quickly, and responses are generally short lived. In vertebrates, the hypothalamus is the neural control center for all endocrine systems.Special features of endocrine glands are, in general, their ductless nature, their vascularity, and commonly the presence of intracellular vacuoles or granules that store their hormones. In contrast, exocrine glands, such as salivary glands, sweat glands, and glands within the gastrointestinal tract, tend to be much less vascular and have ducts or a hollow lumen. In addition to the specialised endocrine organs mentioned above, many other organs that are part of other body systems, such as the kidney, liver, heart and gonads, have secondary endocrine functions. For example the kidney secretes endocrine hormones such as erythropoietin and renin. The field of study dealing with the endocrine system, its disorders, and its specific secretions (hormones) is endocrinology. (Nelson 2005 and Nussey 2001)

Hormones: Are chemical signals produced by specialized cells, secreted into the blood stream, and carried to a target tissue. The target tissue is usually, but not always, located some distance from the secretary cells and contains receptor site for particular hormone. Ultimately, cellular function is regulated through hormonal interaction. (Bishop, 2010)

1.2.1.1 Hypothalamus:

Is a portion of the brain that contains a number of small nuclei with a variety of functions One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland. The hypothalamus is responsible for certain metabolic processes and other activities of the autonomic nervous system. It synthesizes and secretes certain neurohormones, often called releasing hormones or

hypothalamic hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones. Findings have suggested that thyroid hormone (T4) is taken up by the hypothalamic glial cells in the infundibular nucleus/ median eminence, and that it is here converted into T3 by the type 2 deiodinase (D2). Subsequent to this, Triiodothyronine (T3) is transported into the thyrotropin-releasing hormone (TRH)-producing neurons in the paraventricular nucleus. Thyroid hormone receptors have been found in these neurons, indicating that they are indeed sensitive to T3 stimuli. In addition, these neurons expressed a thyroid hormone transporter, supporting the theory that T3 is transported into them. T3 could then bind to the thyroid hormone receptor in these neurons and affect the production of thyrotropin-releasing hormone, there by regulating thyroid hormone production. (Filers, 2006)

1.2.1.2 Pituitary gland:

Pituitary gland is located in small cavity in the sphenoid bone of the skull. The pituitary stalk contains nerve fibres and small blood vessels and connects the pituitary gland to hypothalamus. The pituitary gland is divided into two distinct lobes; the posterior pituitary comprises of nervous tissue and is also known as the neurohypophysis, the anterior pituitary also known as adenohypophysis, consists of glandular epithelial cell. The pituitary gland comprises at least five cell types. The somatotropes secrete growth hormone (GH), the lactotropes secrete porlactin (PRL), thyrotropes secrete Thyroid Stimulating hormone (TSH), gonadotropes secrete lutinizing hormone (LH) and follicle stimulating hormone (FSH) and corticotropes secrete adenocorticotropic hormone (ACTH). These hormones are peptides (ACTH, GH, and PRL) or glycoprotein (TSH, LH, and FSH). (Filers, 2006)

1.2.1.3 Thyroid gland:

Thyroid gland is responsible for the production of two hormones: thyroid hormone and calcitonin. Calcitonin is secreted by parafollicular C cell and is involved in calcium homeostasis. Thyroid hormone regulates body metabolism, neurologic development, and numerous other body functions. Clinically, conditions affecting thyroid hormone level are much more common than those affecting calcitonin. (Bishop, 2010)

1.2.1.3.1 Thyroid anatomy and development:

Thyroid gland is positioned in the lower anterior neck and is shaped like a butterfly. It is made up of two lobes that rest on each side of the trachea, with a band of thyroid tissue – called the isthmus- running anterior to the trachea and bridging the lobes. Posterior to the thyroid gland are the parathyroid glands that regulate serum calcium levels. The fetal thyroid develops from out pouching of foregut at the base of the tongue and migrates to its normal location over the thyroid cartilage in the first 4-8 weeks of gestation. By week 11 of gestation, the thyroid gland begins to produce measurable amounts of thyroid hormone. Thyroid hormone is critical to neurologic development of the fetus. There are two types of cells form thyroid: the follicular (or cuboidal) and parafollicular cells. The follicular cells are secretary and produce Thyroxine (T4) and Triiodothyronine (T3). Each follicle is in shape of a sphere and surrounds a colloid matrix called thyroglobulin. The parafollicular cells, or C cells, are situated in clusters along interstitial spaces. The C cells produce the polypeptide calcitonin, which is involved in calcium regulation. (Bishop, 2010)

1.2.1.3.2 Thyroid Hormone Synthesis:

Iodine is the most important element in biosynthesis of thyroid hormones. Approximately 150 mg of iodide is absorbed in the intestine each day. The thyroid gland has a very high attraction for iodide and trap about 70 mg/day at the base of the cell by active transport. The iodide is then transported to follicular lumen. The iodide molecule is oxidized by peroxidise, presumably at the interface of the cell and the lumen, to a more reactive form, $I^0 or I^+$. This form combines with a glycoprotein thyroglobulin. Thyroglobulins act as performed matrix containing tyrosyl group to which the reactive iodine attaches to form the hydroxyl residues of monoiodotyrosine (MIT) and diiodotyrosine (DIT). The next step is the enzymatic coupling of iodinated tyrosine molecules, catalyzed by peroxidase, to form T4 or T3. The coupling of two DIT molecules form T4. The coupling of DIT molecules and one MIT molecule result in the formation of T3 (3, 5, 3'- T3) or reverse (rT3), or (3, 3', 5'-T3) However, most rT3 is created by a way of peripheral deiodination of T4 rather than manufacture in thyroid gland. T3 contains two iodine atoms in the tyrosyl ring and one iodine atom in the phenolic ring. On the other hand rT3 have two iodine atom in phenolic ring and one atom in tyrosyl ring. These molecules are stored in thyroglobulin in the thyroid follicle. The stored T3 and T4 can be released by enzymatic cleavage of thyroglobulin molecules.

Release of the iodothyronines involves endocytosis of the thyroglobulin from the follicular lumen and hydrolysis of thyroglobulin by protease and peptidase in epithelial cell to liberate free iodoamino acids (T3, T4, MIT and DIT). Most iodothyronines (T3, T4) are secreted into the blood stream, whereas most iodotyrosines (MIT, DIT) are deiodinated within the thyroid, and iodide is using in producing iodoamino acids. Serum concentration of T4 is about 50 times greater than that of T3 about 80% of circulating of T3 is formed following monodeiodination of T4 in peripheral tissues, especially the liver and kidney, by 5' – deiodinase. Thus T4 can be considered as a pro hormone for T3 production. Approximately 33% of T4 that is secreted by the thyroid each day undergoes monodeiodination to produce T3. Another 40% undergoes monodeiodination in the inner ring to produce rT3. Almost all circulating T4 (~ 99.97%) and T3 (~99.7%) hormones are bound to serum protein. Only 0.03 of T4 and 0.3 of T3 are not bound to protein. These fractions called free T4 (FT4) and free T3 (FT3) are physiologically active portion of thyroid hormones. T3 is most biologically active hormone and is three or four times more potent than T4. T3 is more active because it is not as tightly bound to the serum proteins as T4 and has a greater affinity to target tissue receptors thus diffusing more easily into cells than T4. (Bishop, 2010)

1.2.1.3.3 Proteins bound to thyroid hormones:

When releasing into the circulation, only 0.04% of T4 and 0.4% of T3 are unbound by proteins and available for hormonal activity. The three major binding proteins, in order of significance, are thyroxin-binding globulin (TBG), thyroxin binding prealbumin (TBPA), and albumin. The quantity of T4 and T3in circulation can be significantly affected by the amount of binding protein available for carrying hormone. For example, high esterogen levels during pregnancy lead to thyroxin binding protein production by liver. High TBG level result in higher level of bound thyroid hormone, leading to high level of total T3 and T4. In euthyroid individuals, level of active free thyroid hormone remain in the normal range in some instances, however, measurement of free T4 and free T3 may be necessary to eliminate any confusion caused by abnormal binding protein levels. (Bishop 2010)

1.2.1.3.4 Control of thyroid hormones:

Understanding of hypothalamic –pituitary –thyroid axis is essential for correctly interpreting thyroid function testing. This is central in the regulation of thyroid hormone production testing. This axis is central in the regulation of thyroid hormone production. TRH is synthesized by neurone in the supraventricular nuclei in hypothalamus. When secreted this hormone stimulate cells in the anterior pituitary gland to manufacture and release thyrotropin (TSH). TSH in turn, circulates to the thyroid gland and lead to increase production and release of thyroid hormones. When the hypothalamus and pituitary sense that there is an inadequate amount of thyroid hormones in circulation, TRH and TSH secretion increased and leading to increased thyroid hormone production. If thyroid hormones levels are high, TRH and TSH release will be inhibited, leading to lower level of thyroid hormone production and viceversa if thyroid hormone levels are low, TRH and TSH will release, leading to higher levels of thyroid hormones. This feedback loop requires a normally functioning hypothalamus, pituitary, and thyroid gland, as well as an absence of any interfering agents or agent that mimic TSH action. (Bishop, 2010)

1.2.1.3.5 Action of thyroid hormones:

Once release from thyroid gland, thyroid hormones circulates in bloodstream where free T4 and T3 are available to travel across cells membrane. In the cytoplasm, T4 is deiodinated into T3, the active form of thyroid hormone. T3 combines with its receptor on thyroid hormone-responsive genes, leading to production of messenger RNA that, in turn, leads to production of proteins that influence metabolism and development. Effects of thyroid hormone include tissue growth; brain maturation; increase heat production and increase oxygen consumption by means of regulation of carbohydrate, lipid, and protein metabolism; gastrointestinal regulation; sexual maturation and an increased number of β-adrenergic receptors. Clinically, individuals who have excess thyroid hormone (thyrotoxicosis) will have symptoms of increased metabolism such as tachycardia and tremor, while individuals with hypothyroidism show symptoms of lowered metabolism such as edema and constipation. (Bishop 2010)

1.2.1.3.6 Thyroid Disorders:

Four common thyroid disorders include hypothyroidism, hyperthyroidism, goiter, and Thyroid nodules.

1.2.1.3.6.1 Hypothyroidism:

Hypothyroidism occurs when there are insufficient levels of thyroid hormones to provide metabolic needs at the cellular level. It affects females about four times as often as males. Congenital hypothyroidism exists at a rate of around 1 in 4000 births. However, most patients acquire the disease between age 30 years and 60 years. Deficiency of thyroid hormones causes many metabolic processes to slow down. Symptoms of hypothyroidism include enlargement of thyroid gland –or goiter; impairment of cognition (including memory, speech, attention); fatigue; slowing of mental and physical performance; change in personality; intolerance to cold; constipation; decrease sweating; easy bruising; muscle cramps; and dry skin. Hypothyroidism has been shown to be associated with increased cholesterol, LDL, Lipoprotein, apolipoprotein B, and increase risk of coronary heart disease. (Bishop 2010)

1.2.3.6.1.1Congenital Hypothyroidism/ Cretinism:

Most cases of congenital hypothyroidism results from defects in the development or function of the gland itself. Hormone dysgenesis can also cause congenital hypothyroidism. Such disorders are inherited as autosomal recessive traits that cause impaired thyroid synthesis by way of production of defective enzymes. Secondary (pituitary) or tertiary (hypothalamus) congenital hypothyroidism is rare. Numerous clinical manifestations have been associated with congenital hypothyroidism, also known as cretinism. Among these are puffy face; short, thick neck; narrow fore head; short legs; distended abdomen; dry, mottled skin. Skeletal and mental retard if treatment not begun in early infancy. Because most cases of congenital hypothyroidism are not suspected clinically, it is necessary to screen newborn for early diagnosis using cord blood or capillary blood, usually collected as filter-paper spot and eluted from the paper before assay. (Bishop 2010)

1.2.3.6.1.2 Acquired Hypothyroidism:

Most cases of hypothyroidism result from in adequate production of thyroid hormone from a damaged thyroid gland. There are several causes associated with acquired hypothyroidism: chronic thyroiditis; surgical or radioactive iodine treatment of hyperthyroidism, goiter, or cancer; idiopathic atrophy; and metastatic cancer and other infiltrative disorders.

1.2.3.6.1.3 Chronic autoimmune thyroiditis (Hashimoto's Disease)

With or without goiter, chronic autoimmune thyroiditis, or Hashimoto's disease, is most common cause of primary hypothyroidism. Patient with Hashimoto's disease are euthyroid or hypothyroid. In Hashimoto's disease, there is a massive diffuse infiltration of thyroid by lymphocyte. In addition, plasma cells are abundant, and there is an increased in amount of connective tissue. The condition often an a symptomatic disease caused by an unidentified abnormality in the immune system. This abnormality appears to be genetically determined, because family members of persons with the condition have a high probability of developing the disease. Furthermore, the disease has been associated with certain antigen. The immune system abnormality lead to the production of several thyroid antibodies and lymphocytes sensitised to thyroid antigens and may lead to the destruction of thyroid tissue. ThyroPeroxidase Antibodies (TPO) or antimicrosomal or antibodies can be detected in approximately 95% of patient with goiterous Hashimoto's thyroiditis. (Bishop, 2010)

1.2.3.6.1.4 Miscellaneous Causes of Hypothyroidism:

About one third of the patients receiving treatment for hypothyroidism have had thyroid surgery or radioactive iodine therapy for hyperthyroidism. Grave's disease, the major causes of thyrotoxicosis, may spontaneously terminate in hypothyroidism, presumably as the result of autoimmune thyroid damage. The incidence of hypothyroidism increases with aging, as do level of circulating thyroid auto antibodies. However, symptom of hypothyroidism present more subtly in the elderly population. Hypothyroidism also may result from a lack of TSH or TRH. In secondary hypothyroidism, the patient has a pituitary disorder .A decreased production of TSH may result from pituitary irradiation, intracellular haemorrhage, or Sheehan's syndrome (postpartum pituitary infarction) .Tertiary hypothyroidism or hypothalamic failure may result because of tumors, vascular in sufficiency, infections, infiltrative processes, or trauma. TRH response should be normal in patients with tertiary hypothyroidism. (Bishop, 2010)

1.2.3.6.1.5 Subclinical Hypothyroidism:

Subclinical hypothyroidism occurs when there is a mild elevation of TSH with normal levels of T3, T4, and FT4 in patients showing no symptoms of thyroid disease. One report stated that 20% to 50% of individual appear to develop overt hypothyroidism within 4 years to 8 years. Another concluded that 10% of patients with borderline raised TSH are at risk of becoming overt hypothyroid within 1 year. However, current evidence is inconclusive as to whether subclinical hypothyroidism is linked to hyperlipidemia or cardiac dysfunction.

1.2.3.6.1.6 Laboratory Diagnosis of Hypothyroidism:

The earliest laboratory abnormality noted in primary hypothyroidism is an increased TSH concentration. An elevation of basal TSH, therefore, can be considered the single most sensitive and specific marker for primary hypothyroidism. As hypothyroidism progresses, the indirect FT4I and FT4 levels with decrease. TT4, TT3, and rT3 will also be decrease. ThyroPeroxidase Antibodies (TPO) and antithyroglobulin antibodies can be measured to confirm or rule out autoimmune diseases. Secondary and tertiary hypothyroidism may be present with clinical hypothyroidism or decrease s-TSH TT4 and FT4 levels. Secondary versus tertiary hypothyroidism can be differentiated by the TRH test. TSH levels may also rise in patients who are recovering from severe illness and in newborns. This is transient situation, and the TSH generally returns to normal within few days or weeks. (Bishop 2010)

1.2.3.6.1.7Treatment of hypothyroidism:

Treatment of hypothyroidism, except that caused by iodine deficiency, is administration of L-thyroxin. Proper treatment of subclinical hypothyroidism has been shown to reverse lipid imbalances and improve symptom and psychometric testing. Treatment, however, must be individualized. Cautions regarding treatment of newborns and children must be taken to avoid overtreatment, which can lead to dangers in heart, bone, neurologic development and in the elderly population, in which coronary disease may already exist. Because TSH levels may adjust slowly to treatment, FT4 should be used initially in monitoring recovery from hypothyroidism. (Bishop, 2010)

1.2.3.6.2 Hyperthyroidism:

1.2.3.6.2.1 Thyrotoxicosis:

Hyperthyroidism is a disorder manifested by excessive circulating levels of thyroid hormones. The term thyrotoxicosis is applied to a group of syndromes caused by high level of free thyroid hormone in circulation. Thyrotoxicosis means only that the patient is suffering the metabolic consequences of excessive quantities of thyroid hormone. The symptoms found in thyrotoxicosis are related to the increase metabolic activity in various tissues and increased sensitivity to catecholamines. Symptoms vary widely from few complaints to complete incapacitation. Symptoms may include nervousness; irritability; fine tremor; excessive sweating; tachycardia; palpitation; diarrhoea; oligomenorrhea; amenorrhea loss of muscle mass; loss of fat store; producing in increase in fatty acid; a decrease in cholesterol; LDL; lipoprotein(a); exercise intolerance; easy fatigability; and dyspnoeaon excretion. The hematologic manifestation include a decreased white blood cells count because decrease in neutrophils. Lymphocytosis is also present. (Bishop, 2010)

1.2.3.6.2.2 Causes of Thyrotoxicosis

Causes of thyrotoxicosis can be divided into two:

Graves'disease: The most common cause of thyrotoxicosis is Graves'disease (diffuse toxic goiter). Graves'disease occurs six times more commonly in women than men. It occurs frequently at puberty, during pregnancy, at menopause, or following sever stress. The frequency of Graves'disease in general population is about 0.4%.

Pathogenesis of Graves'disease appears to be related to immunologic defect with genetic implications. It is believed to be autoimmune disorder. Thyroid Stimulating hormone receptor (TSHR) auto antibodies are present in approximately 95% of patients with Graves'disease, TPO in approximately 75%. Other abnormal immunoglobulins are also present in circulation of patient with this disease. Further evidence for Graves'disease being an autoimmune disease include that it occurs more commonly in certain family, and there is increased frequency of HLA-Dr3 haplotypes in patients with Graves'disease than in general population.

Graves'disease appears to be related to production of TSHR antibody that subsequently interacts with TSH receptor of thyroid follicular cell membrane. Iodine up take, synthesis of thyroid hormones, and release of thyroid hormones into the circulation are consequently

stimulated. The production of thyroid hormone un related to body's need. TSH production is inhibited. Graves'disease can be diagnosed by clinical manifestation, laboratory assays, and measurement of antibodies titers. (Bishop, 2010)

Thyroiditis:

Thyroiditis describes an inflammation of the thyroid gland. The disorder has been classified as acute (suppurative), subacute (nonsuppurative), silent (painless) or nonspecific and lymphocytic. Acute thyroiditis caused by bacteria, mycobacterium, fungi, or parasites, and is characterized by abscess. Symptoms include tenderness and swelling of the thyroid, fever, chills, and malaise. This form of thyroiditis is rare, apparently because of the glands inherent resistance to infection manifested by its complete encapsulation, rich blood supply, lymphatic drainage, and high iodine content. TT4 and T3 levels are usually normal. (Bishop, 2010)

1.2.3.6.2.3 Miscellaneous Causes of hyperthyroidism:

Other forms of hyperthyroidism exist. In secondary (pituitary) hyperthyroidism, the TSH must be elevated despite a high level of FT4, due to presences of TSH-secreting pituitary adenoma. Excessive TSH secretion also has been found without evidence of pituitary tumor. This condition may be caused by hyper secretion of TRH (tertiary hyperthyroidism), loss of inhibition of TSH secretion normally produced by excessive levels of thyroid hormone. Trophoblastic tumors may causes thyrotoxicosis. These tumors, such as haydatidiform mole, produce and secrete HCG. By virtue of the molecular structure (alpha subunit being identical), HCG may demonstrate thyroid-stimulating ability. The HCG molecule is mistaken for TSH by the TSH receptor on the follicular cell.

In both toxic Multinodular goiter and toxic nodule, the primary defect appears to be the production of thyroid hormone without TSH stimulation. This condition can be confirmed by thyroid scan. Multinodular may express itself in patient who have been euthyroid for years and then have an increase of circulating iodine concentration. Thyroid nodules are normally found in up to 3% of the general population and usually not associated with production of thyroid antibodies or alteration of thyroid function. Thyroid cancers occur in approximately 0.004% of the population. Calcitonin level is elevated in patient with medullary carcinoma of thyroid. Additionally, although it also can be increased in the number of benign conditions, an elevated serum thyroglobulin level is associated with differentiated thyroid carcinoma and thus is used as thyroid cancer ''tumor marker''.(Bishop 2010)

1.2.3.6.2.3 Subclinical hyperthyroidism:

Subclinical hyperthyroidism occur in patients showing no clinical symptoms of hyperthyroidism, but whose TSH levels are less than 0.1 mU/ml to the lower limit of normal range. Like subclinical hypothyroidism, the abnormality may indicate early evidence of thyroid disease. Subclinical hyperthyroidism can occur in 2% to 4% of euthyroid older patients. With these patients, TSH elevation is usually transient. However, Graves'disease and toxic multinodular goiter have been described as common causes of subclinical hypothyroidism. (Bishop, 2010)

1.2.3.6.2.4 Laboratory Evaluation and treatment of Hyperthyroidism:

When Serum TSH decreases, the diagnosis usually is primary hyperthyroidism, provided that the patient does not have a low FT4, is not taking thyroid hormone and is not seriously ill.
A positive Thyroid stimulating hormone receptor (TSHR-TSI) antibody test can help to confirm suspected hyper thyroidal states. Other expected laboratory results include elevated TT4, THBR4, FT4, and FT4I. The TSH level should be clearly subnormal. The presence of TSHR antibodies is diagnostic for cases of suspected Graves'disease. In cases of subclinical hyper thyroidal, look for the serum TSH (s-TSH) to be low because high sensitivity TSH methods can discriminate between euthyroid and hyperthyroid patients. However, the TRH stimulation tests of thyrotoxic patients. Can still be useful as a confirmatory test in these cases. The condition of hyperthyroidism in which FT4I is normal, s-TSH is normal or suppressed, and FT3I, or FT3 is elevated is termed T3 tyrotoxicosis.
The therapy for hyperthyroidism depends on the cause and severity, and the patient's age and general health. The objective of treatment is to lower the thyroid hormones to normal and to minimize the symptoms. Treatment can be achieved by antithyroid medication, radioiodine ablation, or thyroidectomy. (Bishop, 2010)

1.2.3.6.3 Goiter:

Goiter is a noncancerous enlargement of the thyroid gland. The most common cause of goiter worldwide is iodine deficiency in the diet. In the U.S., where iodized salt provides plenty of iodine, goiter is often caused by (and a symptom of) hyperthyroidism (overactive thyroid). Goiter can affect anyone at any age, especially in areas of the world where foods rich in iodine are in short supply. However, goiters are more common after the age of 50 years and in women, who are more likely to have thyroid disorders. Other risk factors include family

medical history, certain medications, pregnancy, and radiation exposure. If the goiter is not severe, there might not be any symptoms. If the thyroid grows large enough, depending on the size, it may cause one or more of the following symptoms: swelling/tightness in the neck, breathing and/or swallowing difficulties, coughing or wheezing and hoarseness.

1.2.3.6.4 Thyroid Nodules:

Thyroid nodules are growths that form on or in the thyroid gland. The causes are not always known but can include iodine deficiency and Hashimoto's disease. The nodules can be solid or fluid-filled. Most are benign, but they can also be cancerous in a small percentage of cases. As with other thyroid-related problems, nodules are more common in women than men and the risk in both sexes increases with age. Most thyroid nodules do not cause any symptoms. However, if they grow large enough, they can cause swelling in the neck and lead to breathing and swallowing difficulties, pain, and goiter. Some nodules produce thyroid hormone, causing abnormally high levels in the bloodstream. When this happens, symptoms are similar to those of hyperthyroidism and can include: high pulse rate, nervousness, increased appetite, weight loss and clammy skin. Cancer of the thyroid gland is quite rare and occurs in about 5% of thyroid nodules. You might have one or more thyroid nodules for several years before they are determined to be cancerous. People who have received radiation treatment to the head and neck earlier in life, possibly as a remedy for acne, tend to have a higher-than-normal risk of developing thyroid cancer. . (Bishop 2010)

1.2.2 Lipids:

are a group of naturally occurring molecules that include fats, waxes, sterols, fat-soluble vitamins (such as vitamins A, D, E, and K), monoglycerides, diglycerides, triglycerides, phospholipids, and others. The main biological functions of lipids include storing energy, signalling, and acting as structural components of cell membranes. (Fahy *et al., 2009*)

Although the term lipid is sometimes used as a synonym for fats, fats are a subgroup of lipids called triglycerides. Lipids also encompass molecules such as fatty acids and their derivatives (including triglyceride, diglycerides, monoglycerides, and phospholipids), as well as other sterol-containing metabolites such as cholesterol. (Michelle *et al., 1999*)

1.2.2.1 Biological function of Lipids:

1. Membranes formation:

Eukaryotic cells are compartmentalized into membrane-bound organelles that carry out different biological functions. The glycerophospholipids are the main structural component of biological, such as the cellular plasma membrane and the intracellular membranes of organelles; in animal cells the plasma membrane physically separates the intracellular components from the extracellular environment. The glycerophospholipids are amphipathic molecules (containing both hydrophobic and hydrophilic regions) that contain a glycerol core linked to two fatty acid-derived "tails" by ester linkages and to one "head" group by a phosphate ester linkage. While glycerophospholipids are the major component of biological membranes, other non-glyceride lipid components such as sphingomyelin and sterols (mainly cholesterol in animal cell membranes) are also found in biological membranes. (Brasaemle, 2007)

2.Energy storage:

Triglycerides, stored in adipose tissue, are a major form of energy storage both in animals and plants. The adipocyte, or fat cell, is designed for continuous synthesis and breakdown of triglycerides in animals, with breakdown controlled mainly by the activation of hormone-sensitive enzyme lipase.

3. Other functions:

The "fat-soluble" vitamins (A, D, E and K) – which are isoprene-based lipids – are essential nutrients stored in the liver and fatty tissues, with a diverse range of functions. Acyl-carnitines are involved in the transport and metabolism of fatty acids in and out of mitochondria, where they undergo beta oxidation. Polyprenols and their phosphorylated derivatives also play important transport roles, such as transport of oligosaccharides across membranes. Polyprenol phosphate sugars and polyprenol diphosphate sugars function in extra-cytoplasmic glycosylation reactions, in extracellular polysaccharide biosynthesis (for instance, peptidoglycan polymerization in bacteria), and in eukaryotic protein N-glycosylation. Cardiolipins are a subclass of glycerophospholipids containing four acyl chains and three glycerol groups that are particularly abundant in the inner mitochondrial membrane. They are believed to activate enzymes involved with oxidative phosphorylation. Lipids also form the basis of steroid hormones (Indiver *et al* 1991 and Wattel *et al.,* 2005)

1.2.2.2 Cholesterol:

From the Ancient Greek chole- (bile) and stereos (solid) followed by the chemical suffix-*ol* for an alcohol, is an organic molecule. It is a sterol (or modified steroid),and an essential structural component of animal cell membranes that is required to establish proper membrane permeability and fluidity. Cholesterol is thus considered within the class of lipid molecules.

In addition to its importance within cells, cholesterol also serves as a precursor for the biosynthesis of steroid hormones, bile acids, and vitamin D. (Hanukoglu, 1992)

Cholesterol is essential for all animal life; each cell synthesizes it from simpler molecules, a complex 37-step process that starts with the intracellular protein enzyme HMG-CoA reductase. However, normal and particularly high levels of fats (including cholesterol) in the blood circulation, depending on how they are transported within lipoproteins, are strongly associated with the progression of atherosclerosis. For a man of about 68 kg, typical total body-cholesterol synthesis is approximately 1 g per day, and total body content is approximately 35 g, primarily located within the membranes of all the cells of the body. Most ingested cholesterol is esterified, and esterified cholesterol is poorly absorbed. The body also compensates for any absorption of additional cholesterol by reducing cholesterol synthesis. For these reasons, cholesterol intake in food has little, if any, effect on total body

cholesterol content or concentrations of cholesterol in the blood. Cholesterol is recycled. The liver excretes it in a non-esterified form (via bile) into the digestive tract. Typically about 50% of the excreted cholesterol is reabsorbed by the small bowel back into the bloodstream. Plants make cholesterol in very small amounts. Plants manufacture phytosterol (substances chemically similar to cholesterol produced within plants), which can compete with cholesterol for reabsorption in the intestinal tract, thus potentially reducing cholesterol reabsorption. When intestinal lining cells absorb phytosterols, in place of cholesterol, they usually excrete the phytosterol molecules back into the GI tract, an important protective mechanism. (John *et al.,* 2007)

1.2.2.2.1 Function of cholesterol:

Cholesterol is required to build and maintain membranes; it modulates membrane fluidity over the range of physiological temperatures. The hydroxyl group on cholesterol interacts with the polar head groups of the membrane phospholipids and sphingolipids, while the bulky steroid and the hydrocarbon chain are embedded in the membrane, alongside the nonpolar fatty-acid chain of the other lipids. Through the interaction with the phospholipids fatty-acid chains, cholesterol increases membrane packing, which reduces membrane fluidity.(John *et al.,* 2007)

The structure of the tetra cyclic ring of cholesterol contributes to the decreased fluidity of the cell membrane as the molecule is in a trans conformation making all but the side chain of cholesterol rigid and planar. In this structural role, cholesterol reduces the permeability of the plasma membrane to neutral solutes, protons, (positive hydrogen ions) and sodium ions. (Haines, 2001)

Within the cell membrane, cholesterol also functions in intracellular transport, cell signalling and nerve conduction. Cholesterol is essential for the structure and function of invaginated caveolae and clathrin-coated pits, including caveola-dependent and clathrin-dependent endocytosis. The role of cholesterol in such endocytosis can be investigated by using methyl beta cyclodextrin (MβCD) to remove cholesterol from the plasma membrane. Recently, cholesterol has also been implicated in cell signalling processes, assisting in the formation of lipid rafts in the plasma membrane. Lipid raft formation brings receptor proteins in close proximity with high concentrations of second messenger molecules. In many neurons, a myelin sheath, rich in cholesterol, since it is derived from compacted layers of Schwann membrane, provides insulation for more efficient conduction of impulses with in cells; cholesterol is the precursor molecule in several biochemical pathways. In the liver, cholesterol is converted to bile, which is then stored in the gallbladder. Bile contains bile

salts, which solubilize fats in the digestive tract and aid in the intestinal absorption of fat molecules as well as the fat-soluble vitamins, A, D, E, and K. Cholesterol is an important precursor molecule for the synthesis of vitamin D and the steroid hormones, including the adrenal gland hormones cortisol and aldosterone, as well as the sex hormones progesterone, estrogens, and testosterone, and their derivatives. Some research indicates cholesterol may act as an antioxidant. (Incardona 2000 and Pawlina and Ross 2006)

1.2.2.2.2 Dietary sources of cholesterol:

Animal fats are complex mixtures of triglycerides, with lesser amounts of phospholipids and cholesterol. As a consequence, all foods containing animal fat contain cholesterol to varying extents. Major dietary sources of cholesterol include cheese, egg yolks, beef, pork, poultry, fish, and shrimp. Human breast milk also contains significant quantities of cholesterol. From a dietary perspective, cholesterol is not found in significant amounts in plant sources. In addition, plant products such as flax seeds and peanuts contain cholesterol-like compounds called phytosterol, which are believed to compete with cholesterol for absorption in the intestines. (Ostlund *et al.,* 2003)

Fat intake also plays a role in blood-cholesterol levels. This effect is thought to come about by changes in the quantity of cholesterol and lipoproteins that are synthesized by the body. Isocalorically replacing dietary carbohydrates with monounsaturated and polyunsaturated fats has been shown to lower serum LDL and total cholesterol levels and increase serum HDL levels, while replacing carbohydrates with saturated fat was shown to increase HDL, LDL, and total cholesterol levels. Tran's fats have been shown to reduce levels of HDL while increasing levels of LDL. Based on such evidence and evidence implicating low HDL and high LDL levels in cardiovascular disease (see Hypercholesterolemia), many health authorities advocate reducing LDL cholesterol through changes in diet in addition to other lifestyle modifications. The USDA, for example, recommends that those wishing to reduce their cholesterol through a change in diet should aim to consume less than 7% of their daily energy needs from saturated fat and fewer than 200 mg of cholesterol per day. An alternative view is that any reduction to dietary cholesterol intake could be counteracted by the organs compensating to try to keep blood cholesterol levels constant. (Espenshade and Hughes 2007)

1.2.2.2.3 Biosynthesis of cholesterol:

All animal cells manufacture cholesterol with relative production rates varying by cell type and organ function. About 20–25% of total daily cholesterol production occurs in the liver;

other sites of higher synthesis rates include the intestines, adrenal glands, and reproductive organs. Synthesis within the body starts with one molecule of acetyl CoA and one molecule of acetoacetyl-CoA, which are hydrated to form 3-hydroxy-3-methylglutaryl CoA (HMG-CoA). This molecule is then reduced to mevalonate by the enzyme HMG-CoA reductase. This is the regulated, rate-limiting and irreversible step in cholesterol synthesis and is the site of action for the statin drugs (HMG-CoA reductase competitive inhibitors).Mevalonate is then converted to 3-isopentenyl pyrophosphate in three reactions that require ATP. Mevalonate is decarboxylated to isopentenyl pyrophosphate, which is a key metabolite for various biological reactions. Three molecules of isopentenyl pyrophosphate condense to form farnesyl pyrophosphate through the action of geranyl transferase. Two molecules of farnesyl pyrophosphate then condense to form squalene by the action of squalene synthase in the endoplasmic reticulum. (Sadava *et al*., 2011)

Biosynthesis of cholesterol is directly regulated by the cholesterol levels present, though the homeostatic mechanisms involved are only partly understood. A higher intake from food leads to a net decrease in endogenous production, whereas lower intake from food has the opposite effect. The main regulatory mechanism is the sensing of intracellular cholesterol in the endoplasmic reticulum by the protein sterol regulatory element-binding protein 1 and 2 (SREBP). In the presence of cholesterol, SREBP is bound to two other proteins: SCAP (SREBP cleavage activating protein) and Insig1. When cholesterol levels fall, Insig-1 dissociates from the SREBP-SCAP complex, which allows the complex to migrate to the Golgi apparatus. Here SREBP is cleaved by S1P and S2P (site-1 and -2 protease), two enzymes that are activated by SCAP when cholesterol levels are low. The cleaved SREBP then migrates to the nucleus, and acts as a transcription factor to bind to the sterol regulatory element (SRE), which stimulates the transcription of many genes. Among these are the low-density lipoprotein (LDL) receptor and HMG-CoA reductase. The LDL receptor former scavenges circulating LDL from the bloodstream, whereas HMG-CoA reductase leads to an increase of endogenous production of cholesterol. A large part of this signalling pathway was clarified by Dr. Michael. Brown and Dr. Joseph. Goldstein in the 1970s. In 1985, they received the Nobel Prize in Physiology or Medicine for their work. Their subsequent work shows how the SREBP pathway regulates expression of many genes that control lipid formation and metabolism and body fuel allocation. (Ohvo-Rekila *et al* 2002)

Cholesterol synthesis can also be turned off when cholesterol levels are high. HMG-CoA reductase contains both a cytosolic domain (responsible for its catalytic function) and a membrane domain. The membrane domain senses signals for its degradation. Increasing concentrations of cholesterol (and other sterols) cause a change in this domain's oligomerization state, which makes it more susceptible to destruction by the proteosome. This enzyme's activity can also be reduced by phosphorylation by an AMP-activated protein kinase. Because this kinase is activated by AMP, which is produced when ATP is hydrolyzed, it follows that cholesterol synthesis is halted when ATP levels are low. (Tymoczko *et al* 2002)

1.2.2.2.4 Plasma transport and regulation of cholesterol absorption:

Cholesterol is slightly soluble in water; it can dissolve and travel in the water-based bloodstream at exceedingly small concentrations. Since cholesterol is insoluble in blood, it is transported in the circulatory system within lipoproteins, complex discoidal particles that have an exterior composed of amphiphilic proteins and lipids whose outward-facing surfaces are water-soluble and inward-facing surfaces are lipid-soluble; triglycerides and cholesterol esters are carried internally. Phospholipids and cholesterol, being amphipathic, are transported in the surface monolayer of the lipoprotein particle. In addition to provide a soluble means for transporting cholesterol through the blood, lipoproteins have cell-targeting signals that direct the lipids they carry to certain tissues. For this reason, there are several types of lipoproteins in blood, called, in order of increasing density, chylomicrons, very-low densitylipoprotein (VLDL), intermediate-densitylipoprotein(IDL), low densitylipoprotein (LDL), and high-density lipoprotein (HDL). The more lipids and less protein a lipoprotein has, the less dense it is. The cholesterol within all the various lipoproteins is identical, although some cholesterol is carried as the "free" alcohol and some is carried as fatty acyl esters referred to as cholesterol esters. However, the different lipoproteins contain apolipoproteins, which serve as ligands for specific receptors on cell membranes. In this way, the lipoprotein particles are molecular addresses that determine the start- and endpoints for cholesterol transport. (Tymoczko *et al* 2002)

Chylomicrons, the least dense type of cholesterol transport molecules, contain apolipoprotein B-48, apolipoprotein C, and apolipoprotein E in their shells. Chylomicrons are the transporters that carry fats from the intestine to muscle and other tissues that need fatty acids for energy or fat production. Cholesterol that is not used by muscles remains in more cholesterol-rich chylomicron remnants, which are taken up from here to the bloodstream by

the liver. VLDL molecules are produced by the liver and contain excess triacylglycerol and cholesterol that is not required by the liver for synthesis of bile acids. These molecules contain apolipoprotein B100 and apolipoprotein E in their shells. During transport in the bloodstream, the blood vessels cleave and absorb more triacylglycerol from IDL molecules, which contain an even higher percentage of cholesterol. The IDL molecules have two possible fates: Half are metabolized by HTGL, taken up by the LDL receptor on the liver cell surfaces, and the other half continue to lose triacylglycerols in the bloodstream until they form LDL molecules, which have the highest percentage of cholesterol within them.LDL molecules, therefore, are the major carriers of cholesterol in the blood, and each one contains approximately 1,500 molecules of cholesterol ester. The shell of the LDL molecule contains just one molecule of apolipoprotein B100, which is recognized by the LDL receptor in peripheral tissues. Upon binding of apolipoprotein B100, many LDL receptors become localized in clathrin-coated pits. Both the LDL and its receptor are internalized by endocytosis to form a vesicle within the cell. The vesicle then fuses with a lysosome, which has an enzyme called lysosomal acid lipase that hydrolyzes the cholesterol esters. Now within the cell, the cholesterol can be used for membrane biosynthesis or esterified and stored within the cell, so as to not interfere with cell membranes. (Weingartner *et al.,* 2010)

Synthesis of the LDL receptor is regulated by SREBP, the same regulatory protein as was used to control synthesis of cholesterol de novo in response to cholesterol presence in the cell. When the cell has abundant cholesterol, LDL receptor synthesis is blocked so new cholesterol in the form of LDL molecules cannot be taken up. On the converse, more LDL receptors are made when the cell is deficient in cholesterol. When this system is deregulated, many LDL molecules appear in the blood without receptors on the peripheral tissues. These LDL molecules are oxidized and taken up by macrophages, which become engorged and form foam cells. These cells often become trapped in the walls of blood vessels and contribute to atherosclerotic plaque formation. Differences in cholesterol homeostasis affect the development of early atherosclerosis (carotid intima-media thickness). These plaques are the main causes of heart attacks, strokes, and other serious medical problems, leading to the association of so-called LDL cholesterol (actually a lipoprotein) with "bad" cholesterol. (Weingartner *et al* 2010)

HDL particles are thought to transport cholesterol back to the liver for excretion or to other tissues that use cholesterol to synthesize hormones in a process known as reverse cholesterol transport (RCT). Having large numbers of large HDL particles correlates with better health

outcomes. In contrast, having small numbers of large HDL particles is independently associated with atheromatous disease progression in the arteries. (Subramaniam *et al* 2011)

1.2.2.2.5 Metabolism, recycling and excretion of cholesterol:

Cholesterol is susceptible to oxidation and easily forms oxygenated derivatives known as oxysterols. Three different mechanisms can form these; autoxidation, secondary oxidation to lipid peroxidation, and cholesterol-metabolizing enzyme oxidation. A great interest in oxysterols arose when they were shown to exert inhibitory actions on cholesterol biosynthesis. This finding became known as the "oxysterols hypothesis". Additional roles for oxysterols in human physiology include there: participation in bile acid biosynthesis, function as transport forms of cholesterol, and regulation of gene transcription.(Lewis and Rader 2005)

In biochemical experiments radio labelled forms of cholesterol, such as tritiated-cholesterol are used. These derivatives undergo degradation upon storage and it is essential to purify cholesterol prior to use. Cholesterol can be purified using small Sephadex LH-20 columns.

Cholesterol is oxidized by the liver into a variety of bile acids. These, in turn, are conjugated with glycine, taurine, glucuronic acid, or sulphate. A mixture of conjugated and nonconjugated bile acids, along with cholesterol itself, is excreted from the liver into the bile. Approximately 95% of the bile acids are reabsorbed from the intestines, and the remainder are lost in the feces. The excretion and reabsorption of bile acids forms the basis of the entero hepatic circulation, which is essential for the digestion and absorption of dietary fats. Under certain circumstances, when more concentrated, as in the gallbladder, cholesterol crystallises and is the major constituent of most gallstones. Although, lecithin and bilirubin gallstones also occur, but less frequently every day, up to 1 g of cholesterol enters the colon. This cholesterol originates from the diet, bile, and desquamated intestinal cells, and can be metabolized by the colonic bacteria. Cholesterol is converted mainly into coprostanol, a non absorbable sterol that isin the feces. A cholesterol-reducing bacterium origin has been isolated from human feces. (Maeshall *and* Einarsson 2007 and Gerard *et al* 2007)

1.2.2.2.6 Clinical Significance of cholesterol level:

1.2.2.2.6.1 Hypercholesterolemia:

According to the lipid hypothesis, abnormal cholesterol levels (hypercholesterolemia) actually higher concentrations of LDL particles and lower concentrations of functional HDL particles are strongly associated with cardiovascular disease because these promote atheroma development in arteries (atherosclerosis). This disease process leads to myocardial (heart attack), stroke, and peripheral vascular disease. Since higher blood LDL, especially higher LDL particle concentrations and smaller LDL particle size, contribute to this process more than the cholesterol content of the HDL particles, LDL particles are often termed "bad cholesterol" because they have been linked to atheroma formation. On the other hand, high concentrations of functional HDL, which can remove cholesterol from cells and atheroma, offer protection and are sometimes referred to as "good cholesterol". These balances are mostly genetically determined, but can be changed by body Resistin, a protein secreted by fat tissue, has been shown to increase the production of LDL in human liver cells and also degrades LDL receptors in the liver. As a result, the liver is less able to clear cholesterol from the bloodstream. Resistin accelerates the accumulation of LDL in arteries, increasing the risk of heart disease. Resistin also adversely impacts the effects of statins, the main cholesterol-reducing drug used in the treatment and prevention of cardiovascular disease. (Durrington 2003)

Elevated levels of the lipoprotein fractions, LDL, IDL and VLDL are regarded as atherogenic (prone to cause atherosclerosis). Levels of these fractions, rather than the total cholesterol level, correlate with the extent and progress of atherosclerosis. Conversely, the total cholesterol can be within normal limits, yet be made up primarily of small LDL and small HDL particles, under which conditions atheroma growth rates would still be high. (Lewington *et al.,* 2007)

Elevated cholesterol levels are treated with a strict diet consisting of low saturated fat, trans fat-free, low cholesterol foods, often followed by one of various hypolipidemic agents, such as statins, fibrates, cholesterol absorption inhibitors, nicotinic acid derivatives or bile acid sequestrate. Extreme cases have previously been treated with partial ideal bypass surgery, which has now been superseded by medication. Multiple human trials using HMG-CoA reductase inhibitors, known as statins, have repeatedly confirmed that changing lipoprotein transport patterns from unhealthy to healthier patterns significantly lowers cardiovascular

disease event rates, even for people with cholesterol values currently considered low for adults. Studies have also found that statins reduce atheroma progression. As a result, people with a history of cardiovascular disease may derive benefit from statins irrespective of their cholesterol levels (total cholesterol below5.0 mmol/L [193 mg/dL] and in men without cardiovascular disease, there is benefit from lowering abnormally high cholesterol levels ("primary prevention"). (Nicholls 2008)

1.2.2.2.6.2 Hypocholesterolemia:

Abnormally low levels of cholesterol are termed hypocholesterolemia. Research into the causes of this state is relatively limited, but some studies suggest a link with depression, cancer, and cerebral haemorrhage. In general, the low cholesterol levels seem to be a consequence, rather than a cause, of an underlying illness. A genetic defect in cholesterol synthesis causes Smith-Lemli-Opitz syndrome, which is often associated with low plasma cholesterol levels. (Wang *et al.,* 2009)

1.2.3 Effects of Thyroid Dysfunction on Lipids:

Thyroid hormones are important modulator of intermediary metabolism. They affect synthesis, mobilization and degradation of lipids, although degradation is influenced more than synthesis. Consequently, thyroid dysfunction particularly hypothyroidism is associated with dyslipidemia which increase the risk of endothelial dysfunction, hypertension and cardiovascular diseases. Hypothyroidism, like obesity is one of the pathological conditions most frequently associated with disorders of lipid metabolism.

Thyroid hormones induce the 3-hydroxy-3-methylglutaryl- coenzyme A (HMG-CoA) reductase, which is the first step in cholesterol biosynthesis. Although decreased thyroid function is accompanied by reduced activity of HMG-CoA reductase, TC and LDL-C levels are increased in patients with hypothyroidism. This is due to the decreased LDL-receptors' activity, resulting in decreased catabolism of LDL and IDL. (Walton *et al* 1965)

Moreover, a decrease in LPL activity is found in hypothyroidism, decreasing the clearance of Tg and LDL. Moreover, decreased activity of the CETP results in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL-C levels. (Santamarina-Fojo *et al* 2004)

Triiodothyronine (T3) upregulates LDL receptors by controlling the LDL receptor gene activation. This T3-mediated gene activation is done by the direct binding of T3 to specific thyroid hormone responsive elements (TREs)Furthermore, T3 controls the sterol regulatory element-binding protein-2 (SREBP-2), which in turn regulates LDL receptor's gene expression (Shin *et al* 2003).

In hyperthyroidism, however, TC and LDL levels were slightly decreased significant statistically. Despite the increased activity of HMG-CoA reductase, the cholesterol levels tend to be decreased in hyperthyroidism due to augmented excretion of cholesterol by bile together with enhanced receptor mediated catabolism of LDL particles. (Duntas, 2002).

Furthermore, hyperthyroidism results in enhanced LDL oxidability, which is related to FT_4 levels. (Costantini *et al* 1998)

1.4 Rationale:

Thyroid diseases (hyperthyroidism and hypothyroidism) are the most abundant endocrine disorder in the world second only to diabetes mellitus.

The increased risk for atherosclerosis and Ischemic heart disease associated with hyperthyroidism and hypothyroidism has been partially attributed to dyslipidemia.

There is limited information on the effect of thyroid hormone disorders on cholesterol and LDL which are consider a significant predictor of atherosclerosis and Ischemic heart disease

Therefore the aim of this study directed to monitor lipid in patients with thyroid hormone disorders and to associate the abnormalities of these hormone with metabolic disorders.

1.5 Objectives:

1.5.1 General objectives:

Assessment serum total cholesterol level of patients with hyperthyroidism and hypothyroidism.

1.5.2 Specific objectives:

1. To measure T3, T4 and TSH hormones in hyperthyroidism and hypothyroidism patients.

2. To measure levels of total cholesterol in patients with hyperthyroidism and patients with hypothyroidism.

3. To compare level of total cholesterol between patients with hyperthyroidism and control.

4. To compare level of total cholesterol between patients with hypothyroidism and control.

5. To correlate total cholesterol level with thyroid hormone tests of patients with hyperthyroidism and hypothyroidism.

CHAPTER TWO

Materials and Methods

2. Materials and Methods

2.1. Materials:

2.1.1. Study design:

This is a Case Control study.

2.1.2. Study area:

Patients with hypothyroidism or hyperthyroidism attended in the Khartoum Teaching Hospital.

2.1.3. Study population:

One hundred patients were enrolled in this study 50 patients were diagnosed as having hyperthyroid and 50 with hypothyroid and 30 apparently healthy subjects with no history of thyroid diseases participated in this study to serve as control.

2.1.4 Inclusion Criteria:

All Patients diagnosed as hypothyroidism or hyperthyroidisms were included in this study.

2.1.5 Exclusion criteria:

All patients with chronic diseases such as renal failure, hypertension and cardiovascular disease and pregnant women that affect in the parameters under study were excluded from this study.

2.1.6 Sample:

Five ml of venous blood was collected from each patient randomly. The sample collected under aseptic conditions and placed in sterile plain containers, after clotting centrifuged for 3 minutes at 3000 rpm to obtain serum, then they obtained serum was kept at $-20^{o}C$ till the time of analysis.

Serum was used to measure T3, T4, TSH and total cholesterol.

2.1.7 Ethical consideration:

Patients who voluntarily accepted to participate in the study were included.

2.1.8 Equipments and disposables:

2.1.8.1 Equipments:

1) TOSOH AIA 600 II, chemistry analyzer.

2) Colorimeter (model JENWAY).

3) Electrical centrifuge (EBA20) serial number: D- 78532.

2.1.8.2 Material:

Plain vaccutainer ,automatic pipettes(100 µl , 1000µl), Hitachi sample cups, absorbent cotton, Sample rack, Disposable syringes, 70% alcohol and Tourniquets.

2.1.8.2.1 Reagents:

1) Cholesterol reagent: Pipes 35mmol/L, sodium cholate 0.5 mmol/L , phenol 28 mmol/L, cholesterol esterase >0.2 U/mL , cholesterol oxidase >0.1 U/mL , peroxidase > 0.8 U/mL , 4-aminoantipyrine 0.5 mmo/L , pH =7.0 .

Cholesterol standard: cholesterol 200mg/dl (5.18mmol/l) .Aqueous primary standard.

2) Thyroid function test reagents (TFT):

1. ST AIA-PACK TT_3, Cat. No. 0025282: Plastic test cups containing lyophilized twelve magnetic beads with anti-T3sheep monoclonal antibody, 125ML of T_3 conjugated to bovine alkaline phosphatase and ANS (8-aninlino-1-naphthalene sulfonic acid) with sodium azid as a preservative.

2. ST AIA-PACK T_4: Cat. No. 0025258: Plastic test cups containing lyophilized twelve magnetic beads with anti-T3sheep monoclonal antibody, 125ML of T_4 conjugated to bovine alkaline phosphatase and ANS (8-aninlino-1-naphthalene sulfonic acid) with sodium azid as a preservative.

3. ST AIA-PACK TSH: Cat. No. 0025281: Plastic test cups containing lyophilized twelve magnetic beads with anti-T3sheep monoclonal antibody, 125ML of TSH conjugated to bovine alkaline phosphatase and ANS (8-aninlino-1-naphthalene sulfonic acid) with sodium azid as a preservative.
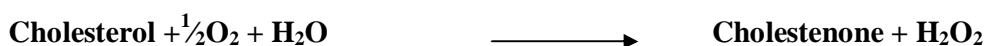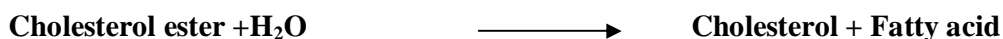
4. Substrate solution.

5. Diluents solution.

6. Washing solution**.**

2.2 Methods:

2.2.1. Estimation of total cholesterol concentration using the enzymatic (Oxidase/Peroxidase) method:

Principle of method:

Free and esterified cholesterol in the sample originates, by means of the coupled reactions described below, a coloured complex that can be measured by spectrophotometer.

$$\text{Cholesterol ester} + H_2O \longrightarrow \text{Cholesterol} + \text{Fatty acid}$$

$$\text{Cholesterol} + \tfrac{1}{2}O_2 + H_2O \longrightarrow \text{Cholestenone} + H_2O_2$$

$$2H_2O + \text{4-Aminoantipyrine} + \text{phenol} \longrightarrow \text{Quinoneimine} + 4\,H_2O$$

Procedure:

1. The reagent was brought to room temperature.
2. Pipetted into a labelled test tube:

Pipette into tube	Blank	Standard	Sample
Sample	_	_	0.01 ml
Standard	_	0.01 ml	_
Reagent	1.0 ml	1.0 ml	1.0 ml

3. Mixed thoroughly and incubate the tubes for 10 minutes at room temperature.
4. Measure the absorbance (A) of the standard and sample at 500 nm against the blank. the colour is stable for at least 2 hours

Calculation:

The cholesterol concentration (mg/dl) =

(A sample/A standard) × Concentration of standard (C) mg/dl

Cholesterol standard provided has been used is 200 mg/dl (5.18mmol/L).

Reference values:

Desirable = up to 200mg/dL=5.2mmol/L.

Borderline High =200-239mg/dL =5.2-6.2mmol/L.

High >240mg/dL => 6.24mmol/L. (Allain,, 1974 and Meiattini *et al* 1978)

2.2.2 Estimation of Thyroid Function Tests (TFT):

Principle of the assay of TT$_3$:

The ST AIA-PACK TT3 is a competitive enzyme immunoassay which is performed entirely in the ST AIA-PACK TT$_3$ test cups. Triiodothyronine, which is displaced from its binding proteins by ANS(8-aninlino-1-naphthalene sulfonic acid), and free T$_3$ present in the test sample compete with enzyme-labeled T$_3$ for a limited number of binding sites on a T$_3$ specific antibody immobilized on magnetic beads. The beads are washed to remove the unbound enzyme-labeled T$_3$ and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The amount of enzyme-labeled T$_3$ that bind to the beads is inversely proportional to the T$_3$ concentration in the test sample. A standard curve using a range of known standard concentration is prepared and unknown T$_3$ concentrations are calculated using this curve.

-Principle of TT$_4$ and TSH are same.

Procedure of TOSOH AIA 600:

1. Allow frozen samples and controls (three levels of commercial lyophilized serum

Control) to reach ambient temperature.

2. Bring the substrate reagent, calibrators if necessary and test cups to room temperature.

3. Sample cups were labelled using a fine-point permanent marker with Sample ID.

4. Diluents solution and wash solution bottle level was checked. Fill the bottles as needed.

5. Empty the waste bottle and solid waste container.

 6. Power on. Wait for Log On screen, Logon by pressing F2 <SKIP> to retain current operator ID

7. Follow the instructions on the Daily Maintenance 1 screen. When complete, press F1

<OK>. Place Substrate in substrate compartment and observe the volume on the Inventory

Screen.

8. When the Daily Maintenance 2 screen appears, place 1 test cup adapter with a

Standardization Cup (STD) on the chain in position 2. Press F1 <START>. Automated

Maintenance will begin.

9. Press the Reagent/Tip Pause key. Refill tip rack and update tip inventory using the keypad

(Only Tosoh brand tips can be used). When finished, move the rack assembly to the left, past

the Sensor. Press the Reagent/Tip Pause key to remove the screen from the display.

10. Press ASSAY MONITOR. Enter sample ID and the control ID, Press ENTER.(For each

run need two sets control, one set is placed in front and other set are place in end).

11. Press ENTER to store tests and sample ID.

12. Repeat above steps for remaining samples.

13. Place appropriate sample cups on the chain with the required test cups

14. Press ASSAY START.

15. The AIA System performs all sample and reagent handling operations automatically. The

AIA Systems read the rate of fluorescence produced by the reaction and automatically

Convert the rate to concentration on ng/mL

Reference range:

Thyroid Stimulating Hormone: 0.4 – 4.5 µg/dl.

Total Triiodothyronine: 0.8 – 1.6 ng/ml.

Thyroxine: 4.9 -11 µg/dl. (Young, 1990)

2.2.3 Quality control:

A control serum was used to monitor the performance of assay procedure: control normal and pathological (Ref.1002120 and 1002210).

If control value was found outside the define range, check the instrument, reagents and calibrator for problems. Each laboratory should establish its own quality control scheme and corrective actions if controls do not meet the acceptable tolerances.

2.2.4 Statistical analysis:

Data was analyzed by using the computer program SPSS version 11.5 to obtain Mean ± SD, Independent T test and correlations. Level of significance was ≤ 0.05.

CHAPTER THREE

Results

3. Results

Hundred patients suffering from thyroid hormone disorders (50 hyperthyroidisms and 50 hypothyroidisms) were attended form Khartoum Teaching Hospital were involved in this study and 30 apparently healthy individual collected as control.

Figure (3.1): Gender distribution in hyperthyroidism and hypothyroidism. Frequency of females patients were more than males. Female constitutes 41% and 38% of hyperthyroidism and hypothyroidism from total hundred patients.

Figure (3.2): Frequency of age group among study groups. Frequency of age group of patients ranged between 15 – 60 years. Most affected age group between 31 – 45 years.

Table (3.1): Show significant differences between the mean of serum total cholesterol, TSH, T3, and T4 in patients with hyperthyroidism compared to control: (128mg/ml ± 30mg/dl) versus (175 mg/d l± 27 mg/dl), (0.08 ng/ml ± 0.3 ng/ml) versus (1.4ng/ml ± 0.9ng/ml), (0.7ng/ml ± 0.4ng/ml) versus (1.1ng/ml ± 0.2ng/ml), and (14.6ng/ml±7.1ng/ml) versus (6.9ng/ml±1.3ng/ml) respectively, P-value= 0.000.

The mean of total cholesterol and TSH was significantly decreased in patients with hyperthyroidism whereas the mean of T3 and T4 was significantly increased.

Table (3.2): Show significant differences between the mean of serum total cholesterol, TSH, T3, and T4 in patient with hypothyroidism compare to control: (198 mg/dl ± 43 mg/dl) versus (175 mg/dl ± 27mg/dl), (39 ng/ml ±41 ng/ml) versus (1.4 ng/ml ±0.9 ng/ml), (0.7 ng/ml ±0.4 ng/ml) versus (1.1 ng/ml ±0.2 ng/ml), and (3.4 ng/ml ±1.7 ng/ml) versus (6.9 ng/ml ±1.3 ng/ml) respectively, P-value = 0.000.

The mean of total cholesterol and TSH was significantly increased in patients with hypothyroidism whereas the mean of T3 and T4 was significantly decreased.

Figure (3.3): A scatter plot showed a significant positive correlation between levels of serum total cholesterol and TSH (r=0.48, P value=0.000).

Figure (3.4): A scatter plot showed a significant negative correlation between levels of serum total cholesterol and T3 (r= -0.57, P value=0.000).

Figure (3.5): A scatter plot shows significant negative correlation between levels of serum total cholesterol and T4(r= -0.59, P value=0.000).

Figure (3.6): A scatter plot showed a significant negative correlation between levels of TSH and T3(r= -0.42, P value=0.000).

Figure (3.7): A scatter plot showed a significant strong positive correlation between levels of T3 and T4(r=0.9, P value=0.000).
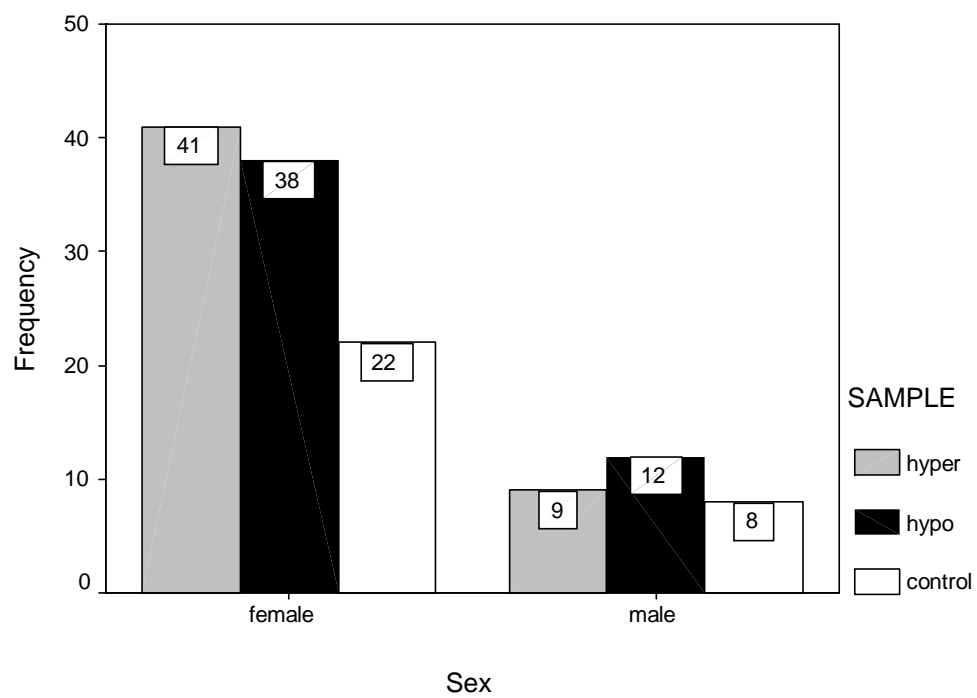
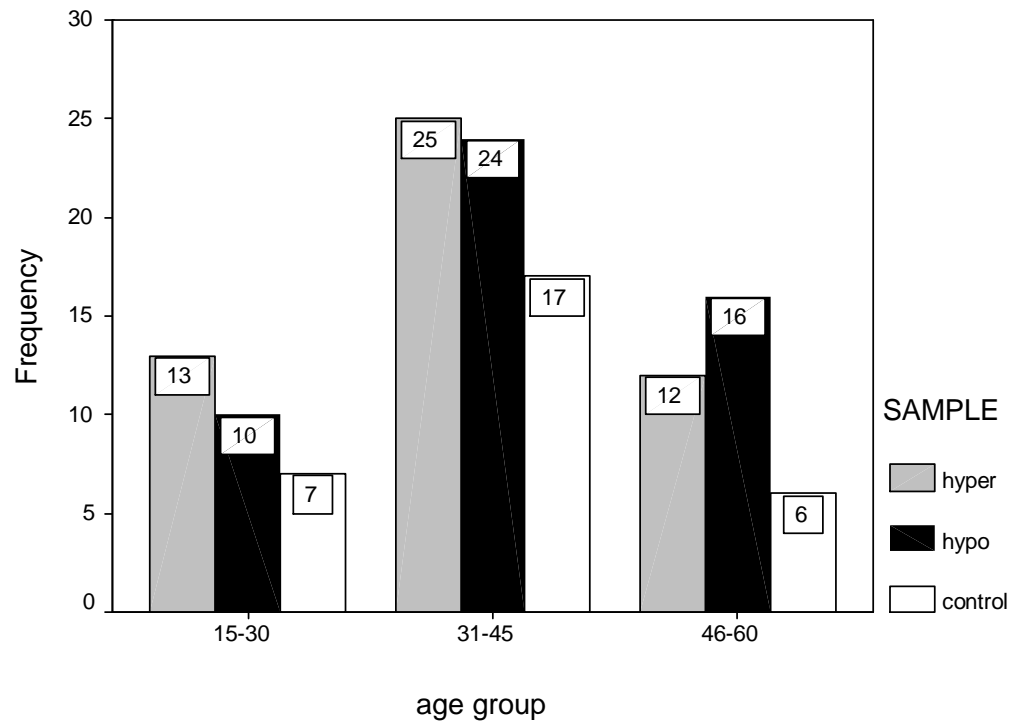**Figure (3.1): Distribution of study group according to gender.**

Figure (3.3): Frequency of age group of population study.

Table (3.1): Serum levels of total cholesterol, T3, T4, and TSH of patients with hyperthyroidism and control group.

Variable	Patient with Hyperthyroidism N=50 (Mean ± SD)	Control N=30 (Mean ± SD)	P .value
Serum Cholesterol (mg/dl)	(128±30)	(175±27)	0.000
TSH (μg/dl)	(0.08±0.3)	(1.4± 0.9)	0.000
T3 (ng/ml)	(3.8±2.5)	(1.1±0.2)	0.000
T4 (μg/dl)	(14.6±7.1)	(6.9±1.3)	0.000

-Independent T-test was used for comparison. P .Value ≤0.05 was considered significant.

Table (3.2): Serum levels of total cholesterol, T3, T4, and TSH of patients with hypothyroidism and control group.

Variable	Patient with Hypothyroidism N=50 (Mean ± SD)	Control N=30 (Mean ± SD)	P .value
Serum Cholesterol (mg/dl)	(198±43)	(175±27)	0.005
TSH (µg/dl)	(39±41)	(1.4±0.9)	0.000
T3 (ng/ml)	(0.7±0.4)	(1.1±0.2)	0.000
T4 (µg/dl)	(3.4±1.7)	(6.9±1.3)	0.000

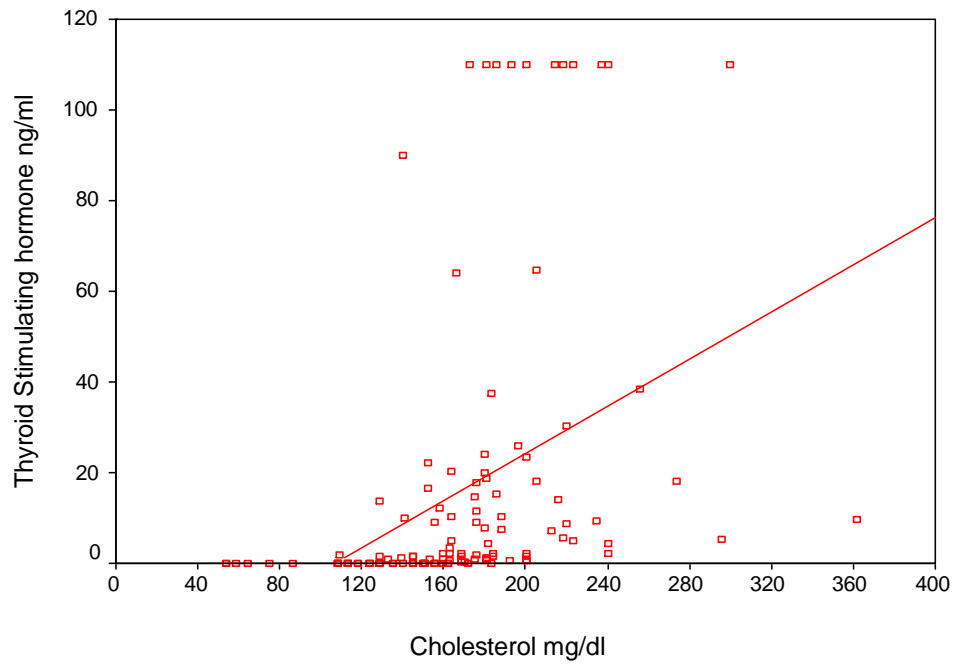-Independent T-test was used for comparison. P .Value ≤0.05 was considered significant.

Figure (3.3): Correlation between levels of serum cholesterol and thyroid stimulating hormone in the study populations(r=0.48, P value=0.000).

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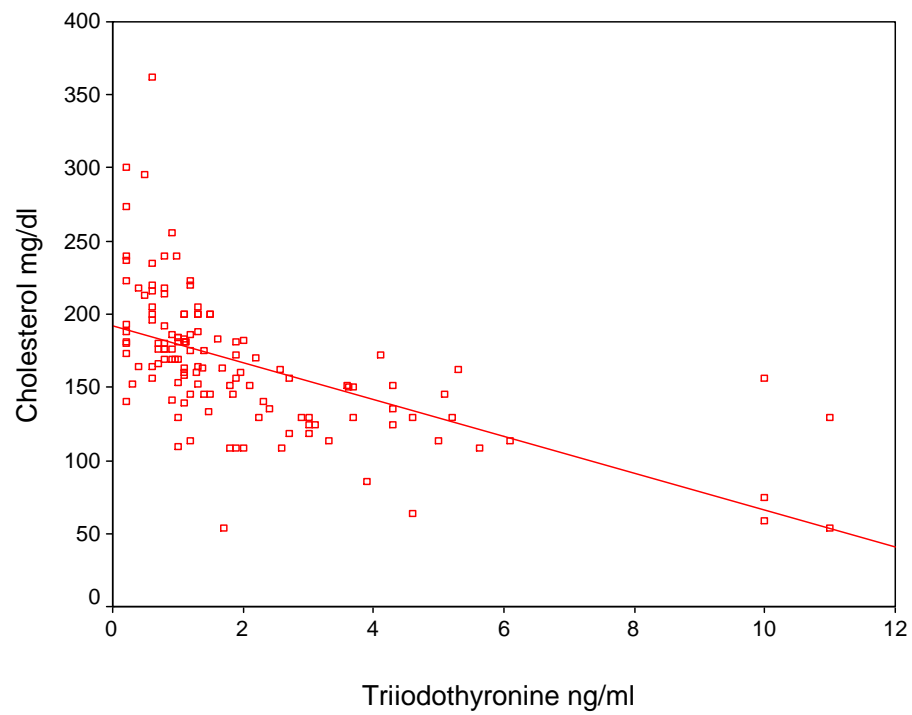**Figure (3.4): Correlation between levels of serum cholesterol and Triiodothyronine in the study populations (r= -0.57, P value=0.000).**
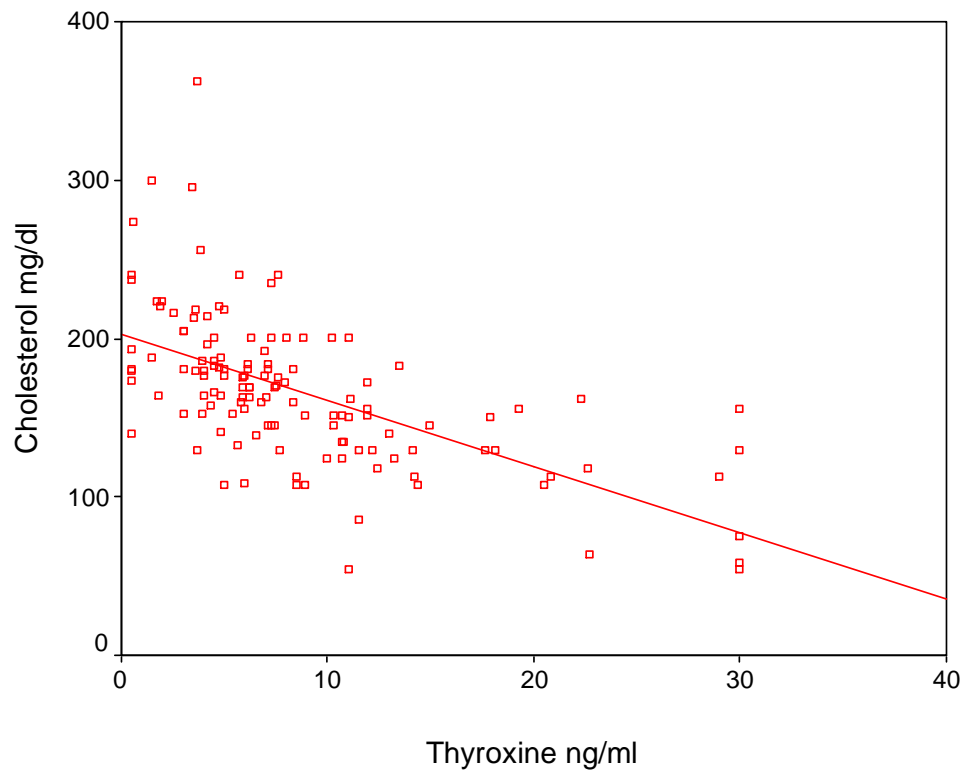
Figure (3.5): Correlation between levels of serum cholesterol and Thyroxine in the study populations (r= -0.59, P value=0.000).

Figure (3.6): Correlation between levels of serum Triiodothyronine and thyroid stimulating hormone in the study populations (r= -0.42, P value=0.000).
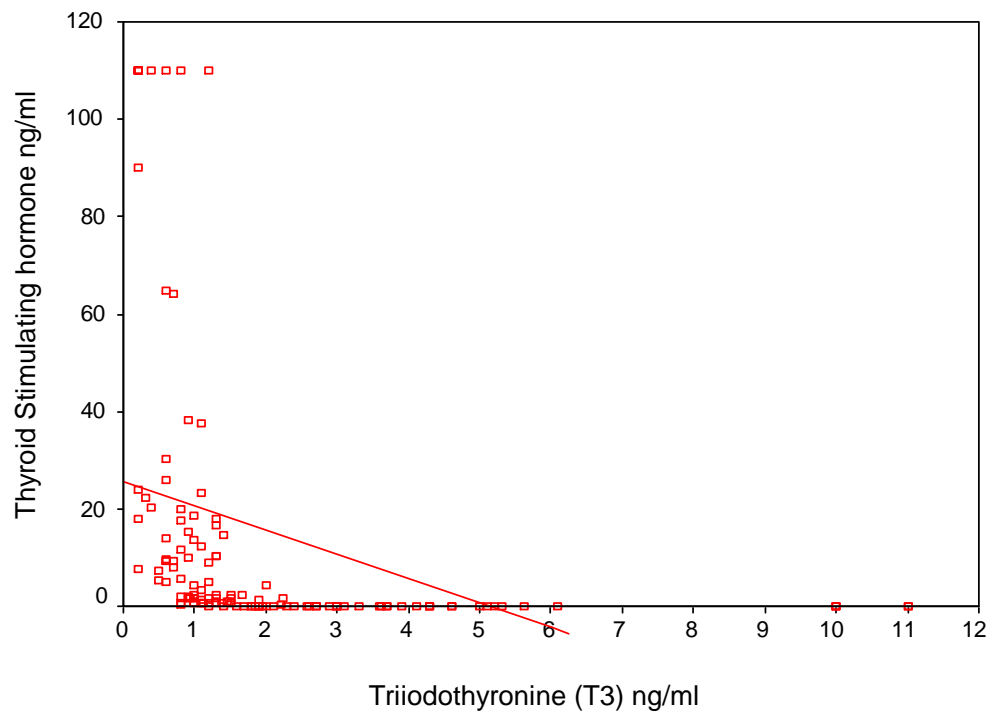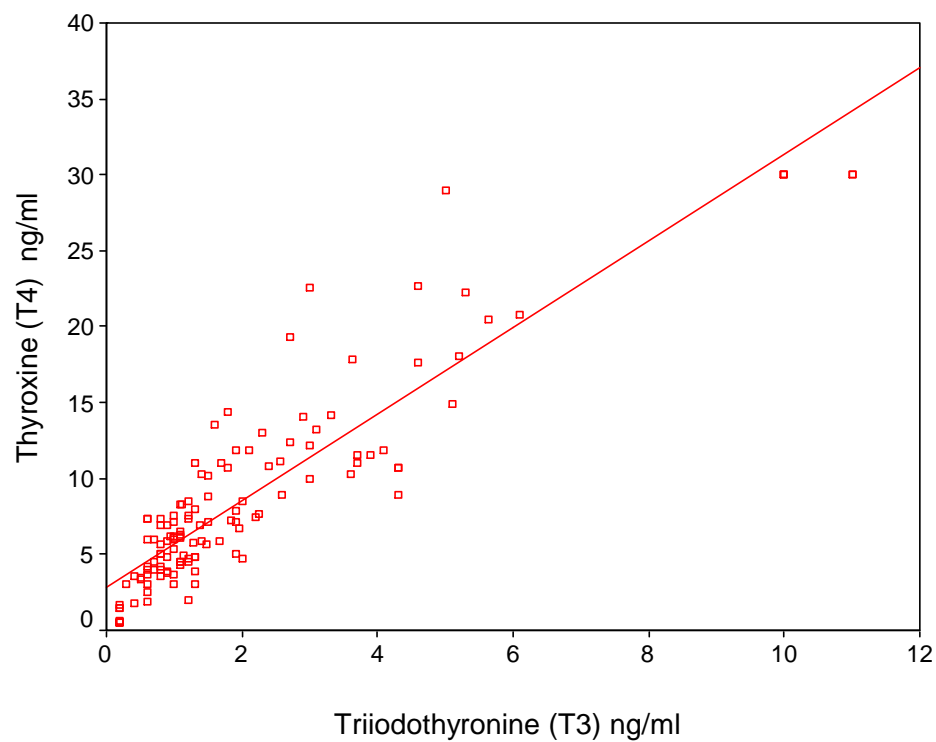
Figure (3.7): Correlation between levels of serum Triiodothyronine and Thyroxine in the study populations (r=0.9, P value=0.000).

CHAPTER FOUR

Conclusion, Discussion and Recommendations

4. Discussions, Conclusions, and Recommendations

4.1 Discussions:

This study was conducted during the period from February 2014 to July 2104 to determine the effect of thyroid diseases on cholesterol levels. Thyroid hormones and total cholesterol were estimated in patients and compared with their levels of control.

From this study I was observed there was higher prevalence of thyroid dysfunction among females compared to males similar to the study of (Sisk 2005).

From this study I was observed that thyroid disorder was more frequently in the age group 30-45 years as that reported by (Holowell *et al.,* 2002).

In the current study the mean value of serum total cholesterol level is significantly decreased in patients with hyperthyroidism when compared to control subject (P value, < 0.05), and these result agreed with Duntas (2002) who reported that the cholesterol levels tend to be increased in hyperthyroidism. Also TSH significantly decreased in hyperthyroid patients when compare to control subject (P value, < 0.05), but the mean of T3 and T4 is significantly increased in patients with hyperthyroidism when compared to control (P value < 0.05).

The mean value of serum total cholesterol level is significantly increased in patients with hypothyroidism when compared to control subject (P value, < 0.05), and these result agreed with (Cabral *et al*., 2004) who reported that there was an association between hypothyroidism and Total cholesterol more than 200 mg/dl.

Also TSH significantly increased in hypothyroid patients when compared to control subject (P value, < 0.05). And the mean of T3 and T4 is significantly decreased in patients with hypothyroidism when compared to control ((P value < 0.05), and these result agreed with (Cabral *et al*., 2004).

Significant positive correlation between the level of serum total cholesterol and levels of TSH was observed in this study (r=0.48, P value= 0.000), The results also showed there a significant negative correlation between levels of serum total cholesterol and levels thyroid hormones (T3 and T4) , (r=-0.57 ,P value =0.000) and(r= -0.59 ,P value= 0.000) respectively,), these results agreed with (McClelland *et al*., 1990) results, their study showed The correlation between serum thyrotropin and cholesterol was highly significant and correlation between increase in serum thyroxine and tri-iodothyronines with the decrease in cholesterol was also highly significant.

There was a significant negative correlation between levels of TSH and T3 (r=-0.42, P value = 0.000). The results showed there is significant strong positive correlation between levels of T3 and T4 (r=0.9, P value=0.000). (Michael, 2010)

In conclusion decreased of thyroid function is accompanied by Total cholesterol and LDL-C levels increased in patients with hypothyroidism this is due to the decreased LDL-receptors activity, resulting in decreased catabolism of cholesterol and LDL. Moreover, a decrease in LPL activity is found in hypothyroidism decreasing the clearance of cholesterol.

Levels of Total Cholesterol, LDL-C tend to decrease in patients with hyperthyroidism. This is due to increased LDL receptor gene expression resulting in enhanced LDL receptor-mediated catabolism of LDL particles. (Walton *et al.,* 1965)

4.2 Conclusions:

From this study we conclude that:

➢ Hypothyroidism and hyperthyroidism are more frequently in female than male.

➢ Thyroid hormone concentrations of T3 and T4 were significantly higher in hyperthyroidism patients compared with control, but TSH was significantly decreased when compared to control.

➢ In hyperthyroid patients there was a significant decrease in the levels of serum total cholesterol.

➢ Thyroid hormone concentrations of T3 and T4 were significantly decreased in hypothyroidism patients compared with control, but TSH was increased when compared to control.

➢ In hypothyroid patients there was a significant increase in the levels of serum total cholesterol.

➢ There is a positive correlation between levels of serum total cholesterol and TSH in both hyperthyroidism and hypothyroidism.

➢ There is a negative correlation between levels of serum total cholesterol and Thyroid hormones (T3 and T4) in both hyperthyroidism and hypothyroidism.

4.3 Recommendations:

From the results of this study we recommended that:

➢ As hypercholesterolemia has been well recognized as major risk factor for cardiovascular disease and hypothyroidism believed to be associated with hyperlipidemia, I will recommend that patients having hypothyroid should be controlled and treated for hyperlipidemia to avoid the risk of atherosclerosis and Ischemic heart disease

➢ Regular follow up and continues measurement of thyroid hormones and lipid of patients with hypothyroidism was recommended.

➢ Fertile young women should be aware the risk of thyroid hormone disorders on fertility.

CHAPTER FIVE

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APPENDICES

بسم الله الرحمن الرحيم

Sudan University of Science and Technology

College of High Graduate

Medical laboratory science

Assessment of Serum Total Cholesterol level in Sudanese's Patients with

Hyperthyroidism or Hypothyroidism

Questionnaire

Serial number (   )

Name: ....

Sex: ....

Age: ....

Treatment: ....

Other Chronic diseases: ....

Lab Investigations:

Test	Result
TSH	.... ng/ml
TT3	...................ng/ml
TT4	...................ng/ml
Cholesterol:	.... mg/dl