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**Assessment of Thyroid Function Tests (T₃, T₄ & TSH)
Among Down Syndrome Patients**

A thesis submitted in partial fulfillment for the requirements of
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الآية

بسم الله الرحمن الرحيم

ولله غيب السماوات والأرض وما أمر الساعة إلا كلمح البصر

أو هو أقرب إن الله على كل شيء قدير (77) والله أخرجكم

من بطون أمهاتكم لا تعلمون شيئاً وجعل لكم السمع والأبصار

والأفئدة لعلكم تشكرون (78)

سورة النحل

Dedication

For soul of my dear father & mother.

Candle of my life.

My brothers & sisters.

The source of my strength.

My friends.

Who support me.

Thank you for your presence in my

Life

ACKNOWLEDGEMENT

Praise to god how gave me the health strength and patience to conduct this study.

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ABSTRACT

Down Syndrome is the most common chromosomal disorder responsible for the majority of mental retardation and deaths in infancy and childhood.⁽¹⁰⁾ This study concerned the relation between Down syndrome and the thyroid disease through estimation thyroid function tests (T₃, T₄ & TSH) , it included 50 participants their ages ranged (7 to 28 years) 48% males and 52% female, and it was carried out in Khartoum , Khartoum State, Sudan in period from (March to July 2018).

The study shown there was significant differences in TSH level with mean \pm SD (2.66 \pm 1.91) ,(1.67 \pm 0.81) in cases and controls respectively with p.value (0.001),also there is significant differences when compare children mean \pm SD(1.88 \pm 1.11) and adults mean \pm SD (2.59 \pm 1.92) with p.value (0.03). There was no significant differences in T₃ level with mean \pm SD(1.04 \pm 0.32),(1.11 \pm 0.86) in cases and controls respectively with p.value (0.08) . There was no significant difference in T₄ level with mean \pm SD (6.09 \pm 2.06) ,(6.40 \pm 1.89) in cases and controls respectively with p.value (0.7). There was no significant differences in T₄ and T₃ levels between age groups. There was no significant differences of TFT between gender .

الخلاصة

متلازمة داون هي أكثر الاضطرابات الصيغية شيوعا وهي سبب رئيسي للتخلف العقلي و عن غالبية الوفيات في مرحلة الطفولة.

تتعلق هذه الدراسة باختبارات تقدير وظائف الغدة الدرقية (T3، TSH & T4) بين المرضى السودانيين المصابين بمتلازمة داون المتراوح أعمارهم بين السابعة الثامنة والعشرين سنة بنسبة مشاركة للذكور (48%) وللاإناث (52%) بولاية الخرطوم بالسودان في الفترة من مارس إلى يوليو لعام 2018. أظهرت الدراسة وجود فروق معنوية في مستوى TSH بمتوسط $2.66 \pm$ (1.91)، (0.81 ± 1.67) في الحالات والضوابط على التوالي وكانت المعنوية (p.value 0.001)، كما توجد فروق ذات دلالة إحصائية عند مقارنة الأطفال بمتوسط (1.11 ± 1.88) والبالغون بمتوسط (1.92 ± 2.59) بمستوى معنوية (p.value 0.03). لم تكن هناك فروق ذات دلالة إحصائية في مستوى T3 بمتوسط (0.32 ± 1.44) ، (0.86 ± 1.11) في الحالات والضوابط على التوالي مع قيمة معنوية (p.value 0.08) كما انه لم يكن هناك اختلاف كبير في مستوى T4 بمتوسط (2.06 ± 6.09) ، (1.89 ± 6.40) في الحالات والضوابط على التوالي وكانت مستوى المعنوية (p.value 0.7) لم تكن هناك فروق ذات دلالة إحصائية في مستويات T3 و T4 بين الفئات العمرية. كما انه لم توجد فروق ذات دلالة إحصائية في مستويات هرمونات TFT بين الجنسين.

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ABBREVIATIONS

AD	Alzheimer disease
ATP	Adenosine Triphosphate
ANTIPO	Antithyroid peroxidase antibodies
BMR	Basal metabolic rate
cAMP	cyclic adenosine monophosphate
CNS	Central nervous system
CMT1A	Charcot – Marie – Tooth disease type 1
CVS	Chorionic villus sampling
D S	Down's syndrome
DIT	Di iodotyrosine
ESR	Erythrocyte sedimentation rate
FT₄I	Free T₄ Index
LDL	Low density lipoprotein
MALDI	Matrix-assisted laser desorption/ionization
MIT	Mono iodotyrosine
PUBS	percutaneous umbilical blood sampling
PPH	Primary pulmonary hypertension
r T₃	reverse T₃
TH	Thyroid hormone
TFT	Thyroid function tests
T₄	Thyroxin
T₃	Triiodotyrosine
TSH	Thyroid stimulating hormone
TRH	Thyrotropin releasing hormone
TREs	Thyroid hormone response elements
TBG	Total binding globulin
TSIs	Thyroid stimulating immunoglobulin's

Chapter One

Introduction

Rationale

Objectives

1.1 Introduction:

Thyroid hormone (TH) are important hormones required for normal maturation of the nervous system in the fetus and infant, secretion and response to growth hormone, required for normal alertness and reflexes at all ages, major determinant of the rate at which the body produces heat during the basal metabolic state increased catabolism of nutrients, facilitates the activity of the sympathetic nervous system by stimulating the synthesis of one class of receptors (beta receptors) for epinephrine and norepinephrine.⁽¹⁾

Thyroid function test (TFT) Laboratory determinations of thyroid function are useful in distinguishing patients with euthyroidism (normal thyroid gland function) from those with hyperthyroidism (increased function) or hypothyroidism (decreased function).⁽²⁾

To understand the thyroid function tests, it is necessary to understand the following basic concepts. The thyroid gland takes iodine from the circulating blood, combines it with the amino acid tyrosine, and converts it to the thyroid hormones thyroxine (T₄) and triiodothyronine (T₃). Iodine composes about two thirds of the weight of the thyroid hormones. The thyroid gland stores T₃ and T₄ until they are released into the bloodstream under the influence of TSH from the pituitary gland. Only a small amount of the hormone is not bound to protein. However, it is the free portion of the thyroid hormones that is the true determinant of the thyroid status of the patient.⁽²⁾

Down syndrome (DS), which is normally caused by trisomy 21, is the most common chromosomal defect. Due to the extensive number of chromosome 21 genes, there is an extremely high incidence of congenital anomalies such as important cardiac and gastrointestinal malformations in individuals with DS. Pericardial effusion is an abnormal accumulation of

fluid in the pericardial cavity that can lead to negative effect on heart function. Massive pericardial effusion in Down syndrome (DS) predominantly correlated with congenital hypothyroidism , but in the pediatric field, it may have correlation with infectious diseases, usually viral infections , acquired and secondary to severe Primary Pulmonary Hypertension (PPH) that is associated with right heart failure.⁽³⁾

1.2 Rationale

D.S patients are large important group in population , and they are need more concern especially they may suffering of many health problems, assessment the health state D.S patients are important to prevent , diagnosed of disease that may affect those patients to decrease the problem and make more healthy life for those very sensitive piece of community. The target of these study is know the health status of patient with Down syndrome through evaluate the thyroid gland functions . Thyriod gland secrete very important hormone for normal organs function metabolism ,growth and general body functions. we going on estimate the main hormones of thyroid gland (T4, T3) and also their stimulance TSH.

1.3 Objectives

1.3.1 General objective:

To evaluate the thyroid function by estimate the general main hormones of thyroid gland among the down syndrome patients.

1.3.2 Specific objectives:

- To assess the thyroid function in Down syndrome patients according to their ages .
- To assess the thyroid function in Down syndrome patients according to their gender .

Chapter Two

Literature Review

2. Literature Review

2.1 Hormones:

Hormones are substances that serve as vehicles for intracellular and extracellular communication. Historically, hormones have been defined as chemical substances that are produced by a gland in one part of the body, are secreted into the bloodstream, and act on a target organ elsewhere.

This has been found to be an oversimplification as hormones are often produced in more than one site and can be transported by mechanisms other than the circulation. In addition, hormones have been found to act on neighboring cells and sometimes even on the very cells in which they were produced.⁽⁴⁾

2.1.1 Classification of hormones:

2.1.1.1 Polypeptide or protein:

Water soluble, circulate freely in plasma as the whole molecule or as active or in active fragments, the half life of these hormones in plasma 10 - 30 minutes or less , wide fluctuations in their concentrations may be seen in sever physiological and pathological circumstances, initiate their response by binding to cell membrane receptors (on or in the cell) and exciting a cellular "second messenger system such as (cycliAMP) within the cell that brings about the specific action of these hormones.⁽⁵⁾

2.1.1.2 steroid hormones:

as example (cortisol and estrogen) , hydrophobic and insoluble in water.⁽⁶⁾ circulate in plasma reversibly bound to transport protein (cortisol binding globulin , sex hormone binding globuline) ,only small fraction free or unbound available to exist physiological action , half life 30 - 90 minutes.⁽⁵⁾

Free steroid hormones enter cell by passive diffusion and bind with intracellular receptors either in cytoplasm or nucleus.⁽⁴⁾

2.1.1.3 Amino acid-related hormones:

water soluble, circulate in plasma.⁽⁴⁾ Either bound to protein (thyroxin) or free (catecholamine's) ,bound form half life are days,free half life are minute or less. Like the water-soluble peptide and protein hormones, these hormones interact with membrane-associated receptors and use a second messenger system .⁽⁵⁾

2.1.2 Hormone receptors: It may be on the cell surface or intracellular within cytoplasm or nucleus.⁽⁴⁾ Provides the very high specificity of the action of hormone.⁽⁵⁾ wich are two types:

2.1.2.1 cell surface receptors:

Peptide hormones bind to cell surface receptors and the conformational change resulting from this binding activates an effectors system , which is inturn responsible for actions of hormone . The intracellular effector that is activated by the hormone receptors interaction is specific G protein (Guanyl-Nucleotide –binding protein).⁽⁶⁾

-The receptor called G protein coupled receptors (GPCRs) , of it the amino terminus is extracellular and the cardoxy terminus intracellular.⁽⁵⁾

2.1.2.2 Intracellular receptors:

-The free hormone of lipid soluble enters the cell via passive diffusion and binds the intracellular receptors in the cytoplasm or nucleus.⁽⁴⁾

-These receptor characterized by hormone binding domain and DNA binding domain .

-The conformation change called activation of the receptor , enables the hormone receptor complex to bind to specific DNA sequence of a target gene permitting control of specific gene expression. ⁽⁵⁾

2.1.3 Measurements of Hormones:

Hormones are measured by a variety of analytical techniques including ; bioassay, receptor assay, immunoassay, and instrumental techniques (such as mass spectrometry inter aced with liquid or gas chromatography).⁽⁷⁾

2.1.3.1 Bioassay Techniques:

Bioassays are based on observations of physiological responses specific or the hormone being measured. In vivo bioassays usually involve the injection of test materials (such as blood or urine from a patient) into suitably prepared animals. Target gland responses such as growth or steroid genesis are then measured. In vitro bioassays involve the incubation of ; tissue, membranes, dispersed cells, or permanent cell lines in a defined culture medium , with subsequent measurement of an appropriate hormone response . Most in vitro bioassays ensure responses proximal or distal to a second messenger such as stimulation of cAMP formation. Bioassay however , tend to be imprecise and are rarely necessary in clinical medicine.⁽⁷⁾

2.1.3.2 Receptor-Based Assays:

Receptor assays depend on the in vitro interaction of a hormone with its biological receptor. In this type of assay, unlabeled hormone displaces trace amounts of labeled hormone from receptor sites. A second approach is to measure a response, such as production of cAMP, when a test sample is added to a preparation that includes the receptor and necessary cofactors. In general, receptor assays are simpler to perform and are more sensitive than bioassays.⁽⁵⁾

Receptor assays also provide an advantage over immunoassays in that they reflect the biological function of a hormone, namely, the capacity to combine with specific receptor sites. By contrast, immunoassays may measure (active hormone, inactive prohormone, hormone polymer, and

metabolites) when all share a common antigenic determinant or set of determinant.⁽⁵⁾

In general, receptor assays are not as sensitive as immunoassays, and enzymes in the biological specimen may degrade the receptor or destroy the labeled tracer. The added complexity and lability of receptor preparations also contribute to the limited application of these assays in the routine clinical laboratory.⁽⁵⁾

2.1.3.3 Immunoassay Techniques:

Immunoassays employing antibodies are widely used to quantify hormones . Currently labeled antibody (Immunometric) assays with nonisotopic labels are the method of choice for measuring most hormones, especially peptides and proteins. Immunometric assays use saturating concentrations of two or more antibodies (often monoclonal) that are prepared against different epitopes of the protein molecule. One of the two antibodies is usually attached to a solid- phase separation system and extracts the hormone from the serum specimen. The second (“detection”) antibody is linked to a signal molecule or “label”. When the second antibody binds to the hormone, a “sandwich” is formed in which the hormone is in the middle, with an antibody on each side at this point the whole sandwich is attached to the solid phase (such as plastic). When more hormone is present, more labeled antibody is able to be bound. After washing away unbound labeled antibody, the label or signal that remains attached to the solid phase is then measured to quantify the bound hormone.⁽⁴⁾

2.1.3.4 Instrumental Techniques:

Mass spectrometers coupled with gas and liquid chromatographs are powerful qualitative and quantitative analytical tools that are widely used to measure hormones. Technical advancements in mass spectrometry

have resulted in the development of matrix-assisted laser desorption/ionization (MALDI) and electrospray ionization techniques that allow sequencing of peptides and mass determination of picomole quantities of analytes. Compared with older methods, mass spectrometry offers greater analytical ; sensitivity, accuracy, speed, and allows simultaneous determination of multiple hormones related to a clinical condition. Mass spectrometric methods are widely available to measure s all molecules such as cortisol and, increasingly are used to measure even large peptide hormones and hormone precursors such as thyroglobulin.⁽⁵⁾

2.2 Thyroid gland :

The thyroid gland is located in the neck, just below the larynx. Its two lobes, each about 5 cm. ⁽²⁾ long, are positioned on either lateral side of the trachea and connected anteriorly by a bridge of tissue called the isthmus.⁽⁸⁾

The thyroid is the largest of the endocrine glands, weighing between 20 and 25 g. It receives an abundant blood supply (80–120 ml/min) through the paired superior thyroid branches of the external carotid arteries and the paired inferior thyroid branches of the subclavian arteries. The venous return is through the paired superior and middlethyroid veins that pass into the internal jugular veins and through the inferior thyroid veins that empty into the brachiocephalic veins.⁽⁸⁾

It is composed of many spherical structures called follicles, each consisting of a single layer of epithelial cells surrounding an extracellular central space. This space is filled with a glycoprotein called thyroglobulin. The follicles secrete the two iodine-containing amine hormones thyroxin (T4) and triiodothyronine (T3) , collectively known as the thyroid hormones (TH), Para follicular cells, which are located between follicles, secrete a third hormone—a peptide called calcitonin;

this hormone does not contain iodine and is not included in the term “thyroid hormones”.⁽¹⁾

2.2.1 Thyroid hormone:

Thyroid hormone is necessary for growth, development, and maintenance of almost all tissues of the body. It stimulates oxidative metabolism and causes the basal metabolic rate (BMR) to increase.⁽⁹⁾

T3 is much more active metabolically than T4, although the thyroid secretes some T3, the majority is produced by deiodination of T4, a process that occurs in nonthyroidal tissue. During starvation, T4 is converted to reverse T3 (rT3), which is not active. Thyroid hormone binds to nuclear receptors and regulates the expression of many genes.⁽⁹⁾

The processes involved in thyroid hormone synthesis and release may be summarized as follows; firstly accumulated iodide is rapidly oxidized to free iodine by a thyroid peroxidase enzyme at the apical surface of the follicular cell, and is then immediately incorporated into the 3- and 5-ring positions of the tyrosine molecules to form monoiodotyrosine (MIT) and diiodotyrosine (DIT) respectively. Coupling of MIT and DIT via an ether linkage then occurs (involving the same thyroid peroxidase enzyme) to form the active hormones T3 (3,5,3'-triiodothyronine) and T4 (3,5,3',5'-tetraiodothyronine or thyroxine). Small amounts (<1%) of the 3,3',5'-triiodothyronine derivative (reverse T3 or rT3) are also synthesized, but this has no significant biological activity. Under conditions of starvation or severe illness, larger amounts of rT3 may be produced relative to T3. During iodination and coupling, the tyrosyl residues remain covalently linked to thyroglobulin molecules at the apical border; (the large thyroglobulin precursor polypeptide is produced continuously as secretory vesicles by the follicular cells, and exocytosed into the colloid through the apical membrane). The thyroid hormones remain in this stored form within the colloid, until they are secreted. Under the influence

of the thyroid stimulating hormone thyrotrophin (TSH), resorption and proteolysis of the stored thyroglobulin-hormone complex within the follicular cells leads to the release of active hormones (ca. 20:1, T4:T3) by diffusion from the basal surface into the local capillary blood supply. Thyroxine is then deiodinated in peripheral tissues (e.g. liver and kidney) to yield the more active T3 (ca. 10 times more potent); MIT, DIT and released iodide are re-utilized for hormone synthesis by the gland. Only minimal amounts of the free thyroglobulin normally escape from the follicles to reach the blood stream. ⁽⁶⁾

2.2.2 Regulation of thyroid hormones:

Thyroid hormone regulated by Hypothalamic-pituitary- thyroid axis, hypothalamus gland secrete Thyrotropin releasing hormone (TRH) which are stimulating pituitary gland to secrete Thyroid stimulating hormone (TSH). ⁽⁵⁾

TSH binding to thyroid epithelial receptors leads to activation of a coupled GS protein and increased intracellular cAMP(cyclic 3',5'-adenosine monophosphate) ; this, in turn, promotes epithelial proliferation, thyroglobulin synthesis and systemic thyroxine (T4) release (with lesser amounts of triiodothyroinine [T3]). T4 and T3 circulate bound to thyroxine-binding globulin (TBG); in the periphery, most free T4 is deiodinated to T3, which binds to nuclear thyroid receptors (TR) in target cells with 10-fold greater affinity than T4 and has proportionately greater activity. Thyroid hormone-TR complexes regulate target gene transcription by binding to thyroid hormone response elements (TREs); the result is a globally augmented basal metabolic rate with broadly increased protein synthesis, as well as carbohydrate and lipid catabolism. Goitrogens diminish T4/T3 synthesis, which increases TSH release, and in turn, causes hyperplastic thyroid enlargement (goiter); propylthiouracil blocks iodide oxidation (blocking thyroid hormone production) and

inhibits T4 de-iodination to T3, while high-dose iodide inhibits thyroglobulin proteolysis. Thyroid parafollicular (C) cells secrete calcitonin; this blocks calcium resorption by osteoclasts and augments skeletal calcium deposition.⁽¹⁰⁾

2.2.3 General function of thyroid hormones:

Thyroid hormones increase the *basal metabolic rate (BMR)* (a measure of O₂ consumption) in virtually all tissues of the body. They stimulate the synthesis of specific proteins involved in *calorigenesis* (heat production) and also influence protein, carbohydrate and fat metabolism.⁽¹⁰⁾

2.2.3.1 Calorigenesis:

Thyroid hormones increase O₂ consumption in all tissues except the brain, testes, anterior pituitary and spleen, which results in increased heat production (through the splitting of ATP molecules) and is therefore important in the process of thermoregulation in a cold environment. It is now believed that this effect (which has a typically long latent period of 4–5 days) may be mediated partly through the synthesis of new Na⁺, K⁺-ATPase (sodium pump) molecules in the cell membranes, and partly via a direct (nongenomic) activation of oxidative phosphorylation in liver mitochondria.

2.2.3.2 Influence on Metabolism:

Carbohydrate metabolism is stimulated both directly (via an increase in gastrointestinal glucose absorption and the synthesis of specific metabolic enzymes) and indirectly by an increase in tissue sensitivity to catecholamines, insulin and growth hormone.⁽¹⁾

The net result is an increase in gluconeogenesis and glycogenolysis in the liver, and glucose utilization by fat, liver and muscle cells. Enhanced glycogenolysis is particularly evident in patients with hyperthyroidism .

Protein metabolism (both resynthesis and degradation) is stimulated when thyroid hormone levels are low; however, at abnormally high levels, protein breakdown predominates (particularly marked in muscle), leading to significant weight loss and elevation in plasma amino acid levels. ⁽¹⁾

Fat metabolism is generally stimulated, but lipolysis is favoured, along with an increased oxidation of free fatty acids. Part of this lipolytic effect is due to potentiation of catecholamine activity on adipose tissue (a β -adrenoceptor effect). Epinephrine causes a large release of fatty acids from adipose tissue, but only in the presence of permissive amounts of thyroid hormone. The major reason is that thyroid hormone facilitates the synthesis of receptors for epinephrine in adipose tissue and so the tissue becomes much more sensitive to epinephrine this phenomenon called (permissiveness).⁽¹⁾

Plasma cholesterol is lowered by thyroid hormones, through an indirect facilitation of liver cholesterol uptake from the blood (increased synthesis of *low-density lipoprotein (LDL)*). ⁽⁶⁾

2.2.3.3 Maturation of the Central Nervous System (CNS):

Thyroid hormones are essential for normal CNS development during late foetal and early postnatal life; the optimal growth of cortical and cerebellar neurons, and the adequate myelination (The axons of some neurons are covered by myelin , which consists of 20 to 200 layers of highly modified plasma membrane wrapped around the axon by a nearby supporting cell of nerve fibres is vitally dependent on their presence. Their absence or deficiency *in utero* or at birth, if not diagnosed early and promptly treated with thyroid hormone replacement, invariably causes irreversible mental retardation (*cretinism*). ⁽¹⁾

2.2.3.4 Skeletal Growth and Maturation:

The actions of thyroid hormone are generally synergistic with those of *growth hormone (GH)*; thyroid hormone is thus essential for normal bone growth and maturation, and the eventual development of normal adult stature. Normal amounts of thyroid hormone are also necessary for proper functioning of the nervous and cardiovascular systems, the gastrointestinal tract, as well as for regular development of the teeth, skin and hair follicles.⁽⁶⁾

2.3 Thyroid disorders:

2.3.1 Hypothyroidism:

is caused by any structural or functional derangement that interferes with adequate thyroid hormone production; overt hypothyroidism affects 0.3% of the population, and subclinical disease occurs in more than 4%.⁽¹⁰⁾

2.3.1.1 Primary hypothyroidism:

vast majority of cases can be accompanied thyroid enlargement (goiter). In iodine-sufficient areas of the world, the most common cause of hypothyroidism is autoimmune thyroiditis (most frequently, Hashimoto thyroiditis); patients typically have circulating anti-microsomal, anti-thyroid peroxidase, and anti-thyroglobulin autoantibodies. Other causes of primary hypothyroidism include dietary iodine deficiency– associated endemic goiter, inborn errors of metabolism, and goitrogens.⁽¹⁰⁾

Genetic causes include: Pendred syndrome (hypothyroidism and sensorineural hearing loss) due to SLC26A4 mutations encoding the pendrin anion transporter on thyroid and inner ear epithelium ,inactivating mutations of the TSH receptor. Hypothyroidism can also follow thyroid surgery or radiation and can be due to infiltrative disorders.⁽¹⁰⁾

2.3.1.2 Secondary hypothyroidism:

is caused by TSH deficiency (or, more rarely, by thyrotropin-releasing hormone [TRH] deficiency). An elevated TSH level is the most sensitive screening test for primary hypothyroidism owing to a loss of feedback inhibition of TRH and TSH production; T4 levels are reduced in any cause of hypothyroidism. Clinical manifestations are cretinism if thyroid deficiency develops in utero through early childhood, and myxedema in older children and adults.⁽¹⁰⁾

Hypothyroidism may affect renal function through direct mechanisms on glomerular and tubular functions and also indirectly through modifications in cardiac and vascular function and derangements in the renin-angiotensin system.⁽¹¹⁾

2.3.2 hyperthyroidism:

The term "hyperthyroidism" encompasses a heterogeneous group of disorders, all characterized by elevated levels of thyroid hormones in the blood.⁽¹²⁾

The most commonly caused by an over activity of the thyroid gland itself resulting from an autoimmune condition known as *Graves' disease*. The serum of such patients contains specific *thyroid-stimulating immunoglobulins (TSIs)* that bind to the TSH receptors on the follicular cells, and like natural TSH, *stimulate* the cells to produce thyroid hormone. Antithyroglobulin and antimicrosomal autoantibodies may also be present. The disease is 5–8 times more prevalent in 40–50 year old females than in males, and is commonly associated with other autoimmune disorders such as myasthenia gravis, Addison's disease, and pernicious anaemia.⁽⁶⁾

2.3.2.1 other causes of primary hyperthyroidism include:

Toxic multinodular goitre can develop from a nontoxic multinodular goitre, which frequently arises in a thyroid that has enlarged due to hyperplasia of the follicular epithelium. The best known cause of multinodular goitre is iodine deficiency.⁽¹³⁾

Activating somatic mutations in the thyrotropin (TSH) receptor have been identified as a cause of hyper functioning thyroid adenomas, and germline mutations have been found in familial nonautoimmune hyperthyroidism and sporadic congenital hyperthyroidism. All mutations reported to date have been located in the transmembrane domain.⁽¹⁴⁾

Subacute (de Quervain's) thyroiditis is a disorder characterized by granulomatous infiltration of the thyroid gland. Clinically, the typical presentation is with local pain, swelling and tenderness, often associated with marked constitutional symptoms and a history of preceding upper respiratory tract infection. The characteristic laboratory findings are of a raised erythrocyte sedimentation rate (ESR), absence of thyroid autoantibodies, and patchy reduced uptake of radionuclide affecting the whole gland on thyroid scanning.⁽¹⁵⁾ It is a self-limiting inflammatory condition of the thyroid, most likely of viral origin, that can follow an upper respiratory tract infection.⁽⁶⁾

Thyrotoxic crisis is an uncommon, life-threatening condition with aggravated toxic symptoms. It occurs most frequently in inadequately or untreated patients with Graves' disease, but has also been described in multinodular toxic goitre. Toxic crisis generally develops relatively rapidly and can occur in all ages and in both men and women.⁽⁶⁾

It is nearly always triggered by factors such as infection, trauma or surgery. Other causes are amiodarone treatment, diabetic ketoacidosis, cerebrovascular incidents, radiation-induced thyroiditis, pre-eclampsia or parturition. A toxic crisis is rarely seen in well-controlled patients with hyperthyroidism.⁽¹⁶⁾

2.3.2.2 Secondary hyperthyroidism may also arise from the following:

Surreptitious (secret) ingestion of excessive amounts of thyroid hormone in an attempt to lose weight (Thyrotoxicosis factitia), TSH-producing pituitary adenoma (rare), ovarian teratoma with thyroid elements (*Struma ovarii*), Metastatic thyroid carcinoma (follicular type) and Treatment with the cardiac anti-arrhythmic drug **amiodarone** (Cordarone X).⁽⁶⁾

2.4 Down's syndrome:

Genomic aneuploidy, defined as an abnormal number of copies of a genomic region, is a common cause of human genetic disorders. Classically, the term aneuploidy was restricted to the presence of supernumerary copies of whole chromosomes (trisomy), or absence of chromosomes (monosomy), but can be extended this definition to include deletions or duplications of subchromosomal regions.

2.4.1 Trisomies:

According to the size of the triplicated genomic region, trisomies can be divided into four categories: complete or whole-chromosome, trisomies; partial trisomies; microtrisomies and triplication of single genes or single functional genomic elements.

Whole-chromosome trisomies : Whole-chromosome trisomies that result from meiotic or mitotic non-disjunction events are common in humans; they account for ~0.3–0.5% of live births. Trisomy for HSA21, which results in Down syndrome and occurs at ~1 in 750 live births, is the most frequent event. Trisomies are often observed in a significant proportion of spontaneous abortions; for example, trisomy 16 is found in 1 out of 13, and trisomy 21 in 1 out of 43 such abortions¹.

2.4.1.1 Partial trisomies:

Partial (or segmental) trisomies that involve a genomic region of more than one chromosomal band are much less frequent than whole-chromosome trisomies. They usually result from abnormal meiosis and segregation in individuals with balanced chromosomal rearrangements. One in about 1,800 newborns have an unbalanced, non-robertsonian rearrangement and approximately half of these are partial trisomies. Unbalanced Robertsonian Translocations with trisomies of the long arms of Acrocentric chromosomes occur in 1 of about 14,000 newborns.

2.4.1.2 Microtrisomies:

This type of trisomy is defined as the partial trisomy of a genomic segment that is shorter than 3–5 Mb and that is not detectable by routine high quality

cytogenetic analysis. It is also known as segmental duplication. The incidence of microtrisomies is, at present, unknown. Most are due to unequal crossovers in meiosis, mediated by the presence of interchromosomal

duplicons or low copy repeats (LCRs; 10–100 Kb each). These duplicons, which make up ~5% of the human genome, promote unequal recombination events that lead to microtrisomies and micromonosomies.

Microduplications are seen, for example, in many cases of Charcot–Marie–Tooth disease, type 1A (CMT1A). This neurological disorder is caused by a ~1.4 Mb duplication of chromosome 17p12, the result of recurrent non-allelic homologous recombination between duplicons that flank the duplicated segment.^{(17, 18).}

2.4.2 general information's of Down syndrome:

This is the most common chromosomal disorder and a major cause of mental retardation. About 95% have a complete extra chromosome 21 (47,XY,21) In 95% of these cases, the extra chromosome is maternal in origin. The incidence is strongly influenced by maternal age: 1 in 1550 births in women younger than 20 years; 1 in 25 births in women older than 45 years. Approximately 4% of all cases have extra chromosomal material derived from a parental chromosome bearing a translocation of the long arm of chromosome 21 to chromosome 22 or 14. Because the fertilized ovum already possesses two normal autosomes 21, the translocated chromosomal fragment provides the same triple-gene dosage as trisomy 21. Such cases are frequently (but not always) familial, because the parent is a carrier of a Robertsonian translocation. Maternal age has no impact. Mosaic variants make up about 1% of all cases; they have a mixture of cells with normal chromosome numbers and cells with an extra chromosome 21. Maternal age has no impact. .^(17, 18)

2.4.2.1 Clinical features include:

Flat facies with oblique palpebral fissures and epicanthic folds ,simian hand crease Severe mental retardation ,40% have congenital heart disease, especially endocardial cushion, defects, responsible for the majority of deaths in infancy and childhood 10- to 20-fold increased risk of acute leukemia.Abnormal immune responses leading to recurrent infections and thyroid autoimmunity also Premature Alzheimer disease (AD).⁽¹⁸⁾

2.4.3 Diagnosis of Down Syndrome:

Down Syndrome can diagnosed Prenatal by (Amniocentesis, Percutaneous umbilical blood sampling (PUBS) and Chorionic villus sampling -CVS) Extraction of fetal cells from maternal circulation. ⁽¹⁸⁾

2.4.3.1 Amniocentesis:

Amniotic fluid is aspirated by means of a needle guided through the mother's abdominal and uterine walls into the amniotic sac. Amniocentesis is preferably performed after the 15th week of pregnancy. By this time, amniotic fluid levels have expanded to 150 mL, so that a 10-mL specimen can be aspirated. If the purpose of amniocentesis is to ascertain fetal maturity, it should be done after the 35th week of gestation. Amniocentesis provides a method to detect fetal abnormalities in situations in which the risk for an abnormality may be high. The test can evaluate fetal hematologic disorders, fetal infections, inborn errors of metabolism, and sex-linked disorders. It is not done to determine the sex of the fetus simply out of curiosity. The development of significant maternal Rh antibody titers or a history of previous erythroblastosis can be an indication for amniocentesis. Chromosomal abnormalities and neural tube defects such as anencephaly, encephalocele, spina bifida, and myelomeningocele can be determined, as can estimates of fetal age, fetal well-being, and pulmonary maturity. Fluorescence in situ hybridization (FISH) technology is useful in the +diagnosis of chromosomal abnormalities or deletion disorders. FISH can identify translocations, inversions, or deletions on chromosomes 13, 18, 21, and X and Y. This technique is most helpful if results are needed quickly for management of pregnancy. ⁽²⁾

2.4.3.2 Percutaneous Umbilical Blood Sampling (PUBS) :

(Cordocentesis Percutaneous umbilical blood sampling (PUBS) is a diagnostic procedure in which fetal blood is drawn from the vein in the umbilical cord. PUBS may be used if ultrasound, amniocentesis, and chorionic villus sampling do not provide adequate information about the fetus. PUBS has somewhat replaced fetoscopy because of the risk factors associated with the latter test. PUBS, for which research is ongoing, is probably a safer and easier way to sample blood from the umbilical cord of the fetus in utero. Fetal blood can be examined for hemophilia, hemoglobinopathies, fetal infections, chromosomal abnormalities, fetal distress, fetal drug levels, and other blood studies. Other common indications include rapid karyotype evaluation, fetal platelet abnormalities, and fetal growth restriction. PUBS is usually performed after 18 weeks' gestation .⁽²⁾

2.4.3.3 Chorionic Villus Sampling (CVS):

Chorionic villus sampling (CVS) can provide very early diagnosis of fetal genetic or biochemical disorders. Some specialists advise that this procedure be reserved for evaluation of conditions that present relatively high genetic risks, such as hemoglobinopathies. CVS involves extraction of a small amount of tissue from the villi of the chorion frondosum. This tissue is composed of rapidly proliferating trophoblastic cells that ultimately form the placenta. Although not a part of the fetus, these villus cells are genetically identical to the fetus and are considered fetal rather than maternal in origin.⁽²⁾

2.5 Previous studies:

2.5.1 Thyroid Function in Young Children With Down Syndrome:

A retrospective review of thyroid function tests (TFTs) was performed on 49 young children (aged 4 months to 3 years) with Down syndrome compared with age-matched controls screened for hypothyroidism because of developmental delay or failure to thrive. Three of the 49 children with Down syndrome had congenital hypothyroidism; of the three, one had Hirschsprung's disease and two had duodenal atresia. Thyroiditis was uncommon, with only two children having thyroid antibodies present: one had acquired hypothyroidism and the other acquired hyperthyroidism. Twenty-seven percent of the Down syndrome cohort had mildly increased thyrotropin (TSH) and normal thyroxine levels. When compared with children with Down syndrome who had normal TFTs, no significant differences in sex, growth rate, maternal age, associated anomalies, developmental or specific thyroid symptoms were present. Transient elevations of TSH level were common in children with Down syndrome whether or not TSH values were initially normal or elevated. Routine neonatal and sequential thyroid screening in young children with Down syndrome is warranted.⁽¹⁹⁾

2.5.2 Natural history of thyroid function in adults with Down syndrome – 10-year follow-up study:

The natural history of thyroid function in adults with Down syndrome (DS) is unknown. This study investigated annual thyroid function tests in 200 adults with DS over a 10-year period. Results Transient and persistent thyroid dysfunction was common. The 5- and 10-year incidence of definite hypothyroidism was 0.9% – 1.64% and 13.6%, respectively. Subclinical hypothyroidism was not found to be an early

sign for definite hypothyroidism. Conclusions Routine screening for adults with DS who are euthyroid can be reduced to every 5 years rather than the present policy of every 1 – 2 years .⁽²⁰⁾

2.5.3 Fifteen-year follow-up of thyroid status in adults with Down syndrome:

The natural history of thyroid function in adults with Down syndrome is relatively unknown with limited long-term follow-up data. This study investigated annual thyroid function tests in 200 adults with Down syndrome over a 15-year period. Results For healthy adults with Down syndrome there is a gradual increase in thyroxine and possible gradual decline in thyroid-stimulating hormone with age. The 15-year incidence for definite hypothyroidism remains low and subclinical hypothyroidism is not a precursor for the onset of definite hypothyroidism .⁽²¹⁾

2.5.4 Thyroid dysfunction in children with Down syndrome:

This article is an evidence-based review of thyroid disease in children with Down syndrome, including a comparison between various professional guidelines for the management of thyroid disease in children with Down syndrome. Aspects of thyroid disease which are discussed include: congenital hypothyroidism; autoimmune thyroid disease; subclinical hypothyroidism; and hyperthyroidism. The national professional guidelines of Ireland, the United Kingdom, the United States of America, Australia and Canada are reviewed and compared. Materials and methods A literature search was conducted using Medline and PubMed. Eighty-nine articles were retrieved and reviewed for inclusion. The guidelines on the medical management of children with Down syndrome of five expert groups have also been retrieved and reviewed for this discussion. These various guidelines offer largely similar advice

regarding frequency of thyroid function tests, with only Ireland and the UK testing less frequently than annually. Only the United Kingdom and Irish Down Syndrome Medical Interest Group guidelines suggest testing for thyroid antibodies at every thyroid screen. None of the guidelines offer suggestions on the optimal course of action to pursue after the discovery of subclinical hypothyroidism. Conclusion In conclusion, more evidence is required regarding the optimal course of treatment for subclinical hypothyroidism. Such evidence may best be obtained by conducting a prospective randomized control trial. ⁽²²⁾

2.5.5 Thyroid dysfunction in a cohort of South African children with Down syndrome:

While international studies show thyroid dysfunction occurs more commonly in individuals with Down syndrome (DS) than in the general population, there is a paucity of available data from sub-Saharan Africa. Objectives: To document the range of thyroid function in a cohort of South African children with DS, and to assess referral and treatment practices when thyroid dysfunction was present. Methods. A retrospective file-based study of 391 children with DS seen at the genetic clinics at three Johannesburg hospitals from 2003 to 2008. Thyroid function test (TFT) results (thyroid-stimulating hormone and free thyroxine) and demographic details were collected for each child. Endocrine clinic files from two of the hospitals were reviewed for additional referral and treatment information. Results: The majority (83.6%) of children had at least one TFT, in most cases performed between the ages of 2 and 12 months. The most common form of thyroid dysfunction was subclinical hypothyroidism (SCH) (28.7%). Up to one-third of the patients, including several neonates with abnormal results, were not referred for further

evaluation and were therefore not receiving the necessary treatment. Interlaboratory biochemical discrepancies and lack of population-specific reference ranges complicated the interpretation of results. The controversy surrounding whether, and how, to treat SCH influenced treatment practices. Thyroid dysfunction is prevalent in South African children with DS. There is an urgent need to address the laboratory biochemical discrepancies, and to establish guidelines for surveillance and treatment to prevent further irreversible neurological and physical impairment .⁽²³⁾

2.5.6 An audit of the management of thyroid disease in children with Down syndrome:

Children with Down syndrome are at a higher risk of thyroid dysfunction than children in the general population. The aim of this audit was to determine thyroid screening practice at University Hospital Limerick and to compare it to the Irish guidelines for the medical management of children with Down syndrome. The thyroid function tests (TFT) of 148 children with Down syndrome were assessed through retrospective database review. Overall compliance with the guidelines was 79/148 (53%), although this varied by age category. The 0-5 years category had a compliance rate of 47/54 (87%), the 6-11 years category was 22/51 (43%), and the 12-17 years category had a compliance rate of 10/43 (23%). The guidelines are effective for monitoring purposes, although performing an annual TFT throughout childhood may be warranted.⁽²⁴⁾

2.5.7 Massive Pericardial Effusion In Down Syndrome With Supravalvar Pulmonary Stenosis Associated To Left Pulmonary Collapse :

Pericardial effusion (PE) in Down syndrome (DS) patients usually occurs secondary to hypothyroidism, but we have no report of massive pericardial effusion in euthyroid Down syndrome patient with supravalvar pulmonary stenosis. Case Presentation: We reported an 11-month-old male with Down syndrome with massive pericardial effusion that had conservative management with levothyroxin who presented with cyanosis, respiratory distress and dominantly left upper lobe pulmonary collapse. There was no response to medical management by antibiotic therapy, O₂ therapy with hood and chest physiotherapy after five days. Pericardiocentesis guided echocardiography performed on the sixth day after admission and 180 cc transudated pericardial fluids has extracted. Clinical and paraclinical findings were relieved dramatically 12-24 hour after pericardiocentesis. However, Angiography showed supravalvar pulmonary stenosis (SPS). Conclusion: We assume that the chronic compression effect of massive pericardial effusion may be a major cause of SPS .⁽³⁾

Chapter Three

Materials and Methods

3. Materials and Methods :

3.1 Study design :

Descriptive case control laboratory based study.

3.2 Study area and duration :

This study was carried out in Khartoum , Khartoum State, Sudan in period from (Maris to July 2018).

3.3 Sampling

3.3.1Sample size :

The study included 30 patients and 20 normal health as control

3.3.2Specimen collection and handling :

Serum and heparinized are used for the assay EDTA and citrate plasma . When using a serum , a venous blood sample is collected aseptically without additives. Store at 18-25 c until a clot has formed (usually 15-45 min), then centrifuge to obtain the serum specimen for assay.

When using heparinized plasma , a venous blood sample is collected aseptically with designated additive. Centrifuge and separate plasma from the packed cells as soon as possible. Samples containing inhibitors of alkaline phosphatase may cause erroneous results. Inspect all samples for air bubbles and foaming. Remove any air bubbles prior to assay.

The sample required for analysis is (10 µl for T4 , 100 µl for TSH and 25 µl for T3) .

3.4 Data Collection tools:

Questionnaire was used for information (eg: name ,age, sex ,location ..).

3.5 Study variables:

- Ages
- sex

3.6 Inclusion and Exclusion criteria

3.6.1 Inclusion criteria:

Any volunteer child or adult with DS after agreement of a person who are concerned to participate in the study.

3.6.2 Exclusion criteria:

volunteer under any treatments that affect of T3 T4 TSH levels hav for examples anti arrhythmial drug and patient under thyroid supplement .

3.7 Ethical Considerations :

Ethical approval obtained from University of Shandi research ethical committee. Informed consent was provided to parents of participants and all gave an written consent.

3.8 instrument:

Using full automated TOSOH AIA 360

3.9 methodology:

Estimation of TSH by sing TOSOH AIA 360 based on immunoenzymetric assay which is performed entierly in the ST AIA-PACK TSH test cups See app(1),T3 based on compititve enzyme immunoassay See app (2),and also estimation of T4 based on competitive enzyme immunoassay,See app (3)

3.10 Data analysis:

Data was analyzed and tabulated using the (Statistical Package for Social Sciences) (SPSS), program version 19, independent t –test .P-value < 0.05 considered significant.

Chapter Four

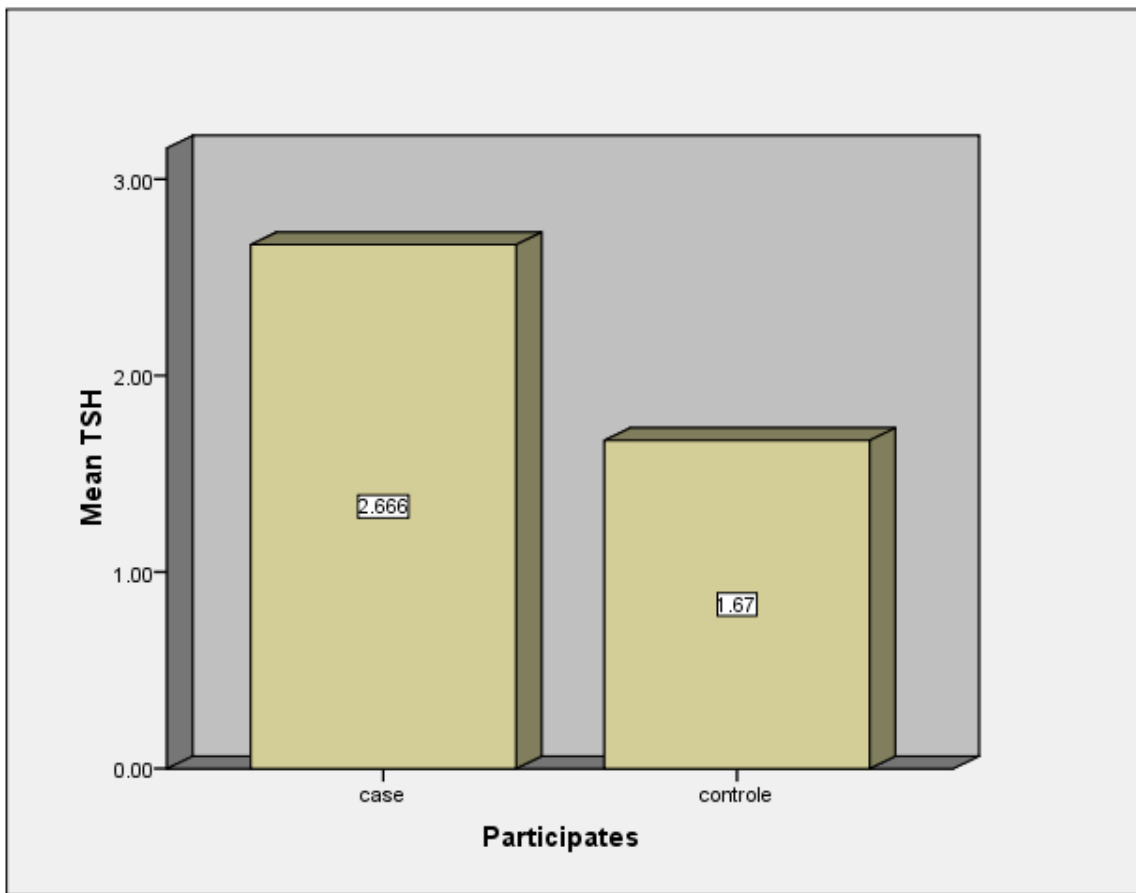
Results

4. Results

Table (4-1) : Mean and S.td of T₄, T₃ and TSH in case group (down syndrome patient) and control normal group (health individual)

Parameter	Case	control	P.value
T₄	6.09 ± 2.06	6.40 ± 1.89	0.70
T₃	1.04 ± 0.32	1.11 ± 0.86	0.08
TSH	2.66 ± 1.91	1.67 ± 0.81	0.001

comparision of mean TSH between participates



Figure(4.1.1) comparison mean of TSH between participates

Table (4-2):comparison of mean and st.d of T₄ T₃ and TSH between the age group(children and adult) of down syndrome patient

Parameter	Children (7-17)	Adult (18-28)	P . value
T₄	6.49 ± 2.25	5.98 ± 1.73	0.3
T₃	1.11 ± 0.28	1.04 ± 0.26	0.8
TSH	1.88 ± 1.11	2.59 ± 1.92	0.03

comparison mean of TSH between age groups

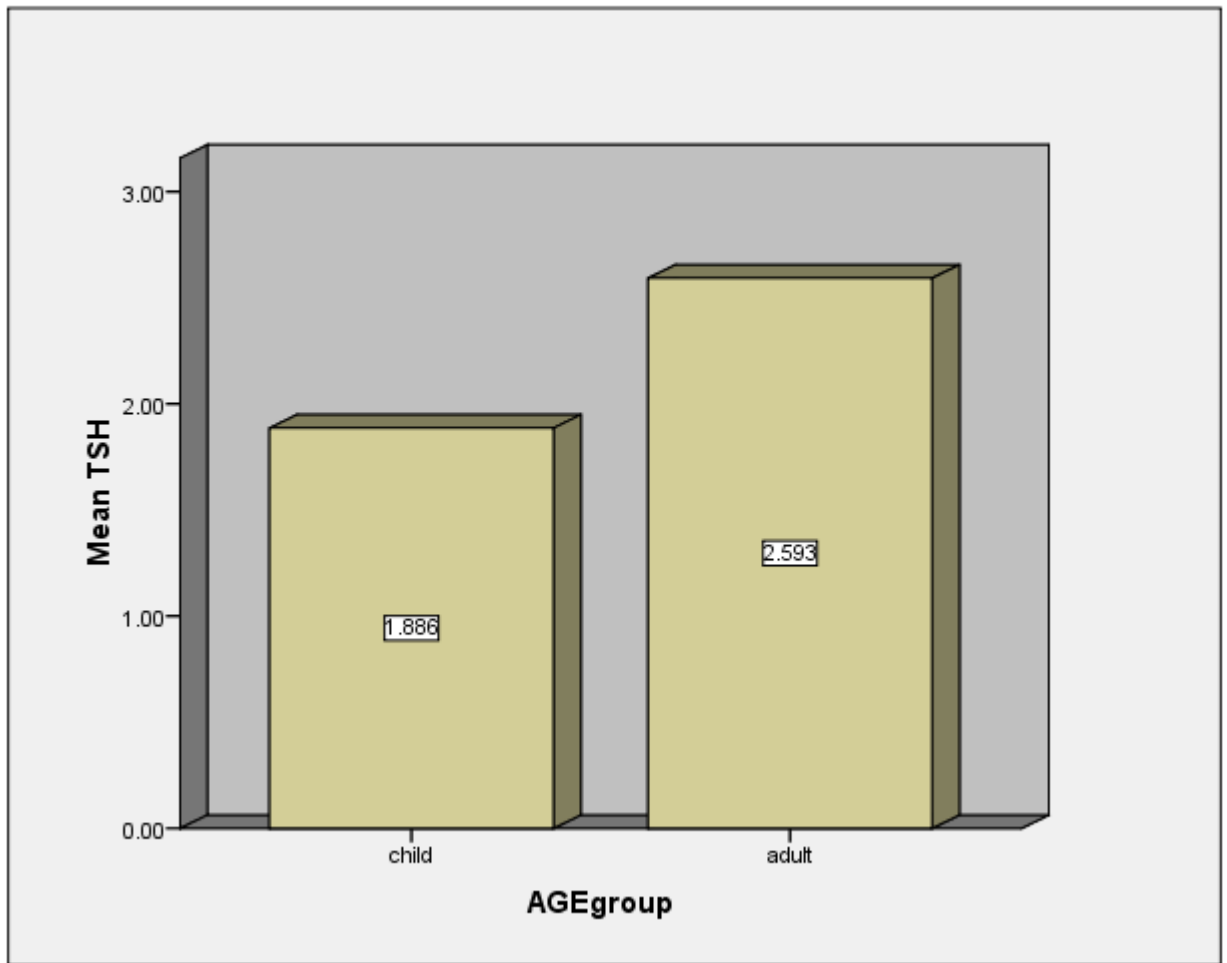


Figure (4.2.1) comparison mean of TSH between age groups

Table (4-3) :comparison of mean and SD of T₄ T₃ and TSH between the gender group of down syndrome patient

Parameter	Male	Female	P . value
T₄	6.40 ± 1.87	6.05 ± 2.10	0.8
T₃	1.12 ± 0.28	1.02 ± 0.25	0.7
TSH	2.24 ± 1.23	2.28 ± 1.95	0.1

-There is no significant differences between males and females and it is agree with (Cutler AT, Benezra-Obeiter R, Brink SJ-1986).

Chapter Five

Discussion

Conclusion

Recommendation

5.1 Discussion :

DS is the most common chromosomal disorder responsible for the majority of mental retardation and deaths in infancy and childhood.⁽¹⁰⁾ This study concerned the relation between Down syndrome and the thyroid disease in Sudanese population, it included 50 participants their ages ranged (7 to 28 years) 48% males and 52% female, and it was carried out in Khartoum, Khartoum State, Sudan in period from (March to July 2018).

The study shown there is significant differences in TSH level (higher in cases than control) with mean (2.66), (1.67) in cases and controls respectively with p.value (0.001), and it is agree with Cutler AT, Benezra-Obeiter R, Brink S in J-1986: the Down syndrome cohort had mildly increased (TSH), Prasher V, Gomez G-2007: DS appear to have high-normal plasma TSH levels., Moosa S, Segal DG, Christianson AL, Gregersen NE-2013: wide spectrum of thyroid dysfunction was represented in this cohort, and disagree with Prasher V, Ninan S, Haque S-2011: gradual decline in thyroid-stimulating hormone with age, it may due to This study was designed to investigate further the natural history of Thyroid dysfunctions in adults with DS over a 15-year period and further recommend the precise frequency of thyroid testing in adults with DS, also sample size have important role.

There is significant differences in TSH level between age group (higher in adults than children) with mean (1.88) for children, and (2.59) for adult, p.value(0.03), and disagree with Prasher V, Ninan S, Haque S-2011: gradual decline in thyroid-stimulating hormone with age.

There is no significant difference in T_3 level with mean (1.04), (1.11) in cases and controls respectively with p.value (0.08).

There is no significant difference in T_4 level with mean (6.09), (6.40) in cases and controls respectively with p.value (0.7), and it is agree partially

with Cutler AT, Benezra-Obeiter R, Brink S in J-1986: Twenty-seven percent of the Down syndrome cohort had normal thyroxine levels, Prasher V, Gomez G-2007: (63%) Down syndrome were euthyroid normal T4, King K, O’Gorman C, Gallagher S, 2014:60% of children of DS with Subclinical hypothyroidism normalT4 , Moosa S, Segal DG, Christianson AL, Gregersen NE-2013:(28.7%)with Subclinical hypothyroidism normalT4. It disagree with Prasher V, Ninan S, Haque S-2011:there is a gradual increase in thyroxine .

There is no significant differences of TFT (T3 ,T4 &TSH)between gender and it agree with Cutler AT, Benezra-Obeiter R, Brink S in J-1986: no significant differences in gender.

5.2 Conclusions

The study concludes that the Down Syndrom patients have higher leveles of TSH than nomal individuelles .

Among Down syndrome patient TSH leveles in adults is higher than childern.

Some pateints may be with slighly increase in TSH and with lower limte of normal range of T_3 and T_4 .

5.3 Recommendations

For all Down syndrome patients should evaluate the thyroid gland functions early as possible by estimated of circulating T4 and T3 level ,Circulating TSH level .

Circulating anti-microsomal, anti-thyroid peroxidase, and anti-thyroglobulin autoantibodies also should be measured due to relation of Down syndrome with thyroid autoimmunity.

Increase sample size and include mother age and estimation lipid profile.

Finally we need more light focusing to those with Down's syndrome in our country in future.

Chapter six

Reference

Appendices

REFERENCES

- .1 Arthur J, Luciano D-S. Human physiology. The mechanisms of body function. 2000.
- .2 Fischbach FT, Dunning MB. A manual of laboratory and diagnostic tests: Lippincott Williams & Wilkins; 2009.
- .3 Tanasan A, Rostampour F, Tanasan P. MASSIVE PERICARDIAL EFFUSION IN DOWN SYNDROME WITH SUPRAVALVAR PULMONARY STENOSIS ASSOCIATED TO LEFT PULMONARY COLLAPSE (CASE REPORT). 2014.
- .4 Arneson WL, Brickell JM. Clinical Chemistry: a laboratory perspective: FA Davis; 2007.
- .5 Burtis CA, Ashwood ER, Bruns DE. Tietz textbook of clinical chemistry and molecular diagnostics-e-book: Elsevier Health Sciences; 2012.
- .6 Constanti A. Basic endocrinology for students of pharmacy and allied health sciences: CRC Press; 1998.
- .7 Hubbard J. A concise review of clinical laboratory science: Lippincott Williams & Wilkins; 2011.
- .8 Moore KL, Dalley AF, Agur AM. Clinically oriented anatomy: Lippincott Williams & Wilkins; 2013.
- .9 Lieberman M, Swanson TA. Biochemistry, molecular biology, and genetics: Wolters Kluwer/Lippincott Williams & Wilkins; 2014.
- .10 Kumar V, Abbas AK, Fausto N, Aster JC. Robbins and Cotran pathologic basis of disease, professional edition e-book: elsevier health sciences; 2014.
- .11 Iglesias P, Bajo MA, Selgas R, Díez JJ. Thyroid dysfunction and kidney disease: an update. Reviews in Endocrine and Metabolic Disorders. 2017;18(1):131-44.

- .12 Singer PA, Cooper DS, Levy EG, Ladenson PW, Braverman LE, Daniels G, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. *Jama*. 1995;273(10):808-12.
- .13 Nyström E, Berg GE, Jansson SK, Tørring O, Valdemarsson SV. Toxic Multinodular Goitre. *Thyroid Disease in Adults*: Springer; 2011. p. 187-93.
- .14 Kopp P, Muirhead S, Jourdain N, Gu W-X, Jameson JL, Rodd C. Congenital hyperthyroidism caused by a solitary toxic adenoma harboring a novel somatic mutation (serine281--> isoleucine) in the extracellular domain of the thyrotropin receptor. *The Journal of clinical investigation*. 1997;100(6):1634-9.
- .15 Ramtoola S, Maisey M. Subacute (de Quervain's) thyroiditis. *The British journal of radiology*. 1988;61(726):515-6.
- .16 Nyström E, Berg GE, Jansson SK, Tørring O, Valdemarsson SV. Thyrotoxic Crisis/Thyroid Storm. *Thyroid Disease in Adults*: Springer; 2011. p. 201-4.
- .17 Antonarakis SE, Lyle R, Dermitzakis ET, Reymond A, Deutsch S. Chromosome 21 and down syndrome: from genomics to pathophysiology. *Nature reviews genetics*. 2004;5(10):725.
- .18 Pentao L, Wise CA, Chinault AC, Patel PI, Lupski JR. Charcot–Marie–Tooth type 1A duplication appears to arise from recombination at repeat sequences flanking the 1.5 Mb monomer unit. *Nature genetics*. 1992;2(4):292.
- .19 Cutler AT, Benezra-Obeiter R, Brink SJ. Thyroid function in young children with Down syndrome. *American Journal of Diseases of Children*. 1986;140(5):479-83.

- .20 Prasher V, Gomez G. Natural history of thyroid function in adults with Down syndrome—10-year follow-up study. *Journal of Intellectual Disability Research*. 2007;51(4):312-7.
- .21 Prasher V, Ninan S, Haque S. Fifteen-year follow-up of thyroid status in adults with Down syndrome. *Journal of Intellectual Disability Research*. 2011;55(4):392-6.
- .22 King K, O’Gorman C, Gallagher S. Thyroid dysfunction in children with Down syndrome: a literature review. *Irish journal of medical science*. 2014;183(1):1-6.
- .23 Moosa S, Segal DG, Christianson AL, Gregersen NE. Thyroid dysfunction in a cohort of South African children with Down syndrome. *SAMJ: South African Medical Journal*. 2013;103(12):966-70.
- .24 King K, O’Gorman C, Gallagher S. An audit of the management of thyroid disease in children with Down syndrome. *Irish medical journal*. 2014.

Appendices

app.(1)

TSH

Principle of the assay :

The ST AIA- PACK TSH is two-site immunoenzymetric assay which is performed entirely in the ST AIA- PACK TSH test cups. TSH present in the test sample is bound to monoclonal antibody and conjugated with bovine alkaline phosphatase in the test cups . The magnetic beads are washed to removed unbound enzyme- labeled monoclonal antibody and are then incubated with fluorogenic substrate , 4-methyleumbelliferyl phosphate (4MUP). The amount of enzyme conjugated with monoclonal antibody that bind to the beads is directly proportional to the TSH concentration in the test sample . A standard curve is constructed , and unknown sample concentration are calculated using this curve .

Material required for TSH measurement :

AIA-pack substrate set II-

AIA-pack substrate reagent II

AIA-pack substrate reconstituent II

AIA-pack TSH 3rd –Gen Calibrator set -

AIA-pack TSH 3rd –Gen Calibrator(1) 0 μ IU/ml

AIA-pack TSH 3rd –Gen Calibrator(2) 0.2 μ IU/ml

AIA-pack TSH 3rd –Gen Calibrator(3) 5 μ IU/ml

AIA-pack TSH 3rd –Gen Calibrator(4) 25 μ IU/ml

AIA-pack TSH 3rd –Gen Calibrator(5) 50 μ IU/ml

AIA-pack TSH 3rd –Gen Calibrator(6) 110 μ IU/ml

- AIA-pack TSH 3rd –Gen sample dilution solution

- AIA-pack Wash concentrate

- AIA-pack Diluent concentrate

-Sample Cups

- AIA-pack Detector standardization test Cup

- AIA-pack Treatment Cup.

Reference interval :

0.4 ----- 3.6 μ IU/ml

app (2)

Triiodothyronine

Principial of test :

The ST AIA – PACK TT3 is compititve enzyme immunoassay which is performed entierly in the ST AIA-PACK TT3 cups. T3 , which is displaced from its binding protein by ANS (8- amino-1- naphthalene sulfonic acid), and free T3 present in the test sample compete with enzyme – labeled T3 for alimeted numder of binding site on a T3 specific antibody immoblized on magnetic beads .The beads washed to remove unbound enzyme –labeled T3 and are then incubated with a fluorogic substrate , 4-methylumbelliferyl phosphate (4-MUP). The amount of enzyme labeled T3 that binds to beads in inversely proportional to the T3concentration in th sample . A standard curve using a range of known standard concentration is prepared and unknownT3 concentrations are calculated using this curve

Material required for T3 measurment :

AIA-pack subustrate set II-

AIA-pack subustrate reagent II

AIA-pack subustrate reconstituent II

AIA-pack TT3 – Calibrator set -

-AIA-pack TT3 Calibrator(1) 0 ng/ml

-AIA-pack TT3 Calibrator(2) 0.5 ng/ml

-AIA-pack TT3 Calibrator(3) 1.0 ng/ml

-AIA-pack TT3 Calibrator(4) 2.0 ng/ml

-AIA-pack TT3 Calibrator(5) 4.5 ng/ml

-AIA-pack TT3 Calibrator(6) 9.0 ng/ml

- AIA-pack TT3 sample dilution solution

- AIA-pack Wash concentrate

- AIA-pack Diluent concentrate

-Sample Cups

- AIA-pack Detector standardization test Cup

- AIA-pack Treatment Cup

Reference interval :

0.79 ----- 1.58 ng/ml

app (3)

Thyroxine (T₄):

Principial of test :

The ST AIA – PACK T₄ is competitive enzyme immunoassay which is performed entirely by the ST AIA – PACK T₄ test cups .Thyroxine , which is displaced from its bind proteins by ANS(8-anilino-1-naphthalene sulfanic acid), and free T₄ present in the test sample compete with enzyme –labeled thyroxine for alimited number of binding sites on a thyroxine-specific antibody immobilized on magnetic beads. The beads are washed to remove the unbound enzyme-labeled thyroxine and are then incubate with a fluorogenic substrste , 4-methylumbelliferyle phosphate (4MUP). The amount of enzyme-labeled thyroxine that binds to the beads is inversely proportional to the thyroxine in the test sample . A standard curve using a range of known standard concentration is constructed and unknown thyroxine concentration are calculated using this curve .

Material required for T4 measurment :

AIA-pack subustrate set II-

AIA-pack subustrate reagent II

AIA-pack subustrate reconstituent II

-AIA-pack TT4 – Calibrator set

-AIA-pack TT4 Calibrator(1) 0 μg/dl

-AIA-pack TT4 Calibrator(2) 0.75 μg/dl

-AIA-pack TT4 Calibrator(3) 3 μg/dl

-AIA-pack TT4 Calibrator(4) 6 μg/dl

-AIA-pack TT4 Calibrator(5) 12 μg/dl

-AIA-pack TT4 Calibrator(6) 26 μg/dl

- AIA-pack TT4 sample dilution solution

- AIA-pack Wash concentrate

- AIA-pack Diluent concentrate
- Sample Cups
- AIA-pack Detector standardization test Cup
- AIA-pack Treatment Cup

Reference interval :

4.9 -----11 $\mu\text{g/dl}$

جامعة شندي – كلية الدراسات العليا

استبانته حول المصابين بملازمة داون

الاسم (اختياري) : رقم الإستبانة : ()

المدرسة : العمر :

المنطقة:.....

*النوع :

أنثى

ذكر

* هل تم فحص هرموني الغدة الدرقية من قبل :

لا

نعم

* ماذا كانت نتائج الفحص :

منخفضة

مرتفعة

طبيعية

* هل يعاني المريض من أي مرض مزمن :

لا نعم

اذكره.....

* هل هنالك مصابون بالمرض في الأسرة :

نعم

لا

* الرجاء كتابة العقاقير الطبية التي يتعاطاها في الوقت الحالي إن وجدت :

نعم

لا

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