Sudan University of Science and Technology

Collage of Graduate Studies

Estimation of D-dimer Level among thyroid abnormalities Sudanese Women at Omdurman locality

قياس مستوي دي دايمر لدى النساء المصابات بخلل وظيفة الغدة الدرقية في محلية امدرمان

A Dissertation Submitted for Partial Fulfillment For the Requirements of the Degree of M.Sc. In Medical Laboratory Science- Hematology and Immunohematology

Submitted by:

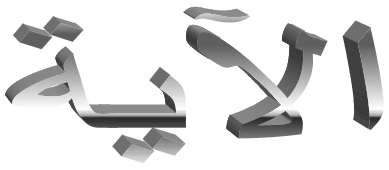
Eiman Abd Algany Ibraheem

B.Sc. (Honor) in Medical Laboratory Science (Hematology and Immunohematology, Sudan University of Science and Technology,2011)

Supervisor:

Dr. Kawthar Abdelgaleil MohamadSalih

2018



بسم الله الرحمن الرحيم

قال تعالي:

(فَتَعَالَى اللَّهُ الْمَلِكُ الْحَقُّ وَلَا تَعْجَلْ بِالْقُرْآنِ مِن قَبْلِ أَن يُقْضَى إِلَيْكَ وَحْيُهُ وَقُل رَّبِّ زِدْنِي عِلْمًا)

صدق الله العظيم

سورة طه - الآية(114)

Dedication

This humble work is dedicated to:

My amazing husband

The moon of my life for his patience and for encouraging me to belief in my self

To my sweet daughter jood

A special feeling of gratitude to my loving parents.

My Mum and my Dad

For earning and honest living for me and for supporting

I also dedicate this dissertation to my friends

Who supporting me throughout the process.

My teachers

Who made it possible by supporting me all the time in shaping and guiding

Acknowledgment

Firstly the greatest thank to Allah from the start to the end , special thank to Dr. Kawthar Abdelgaleil for her supervision, generous supporting and guidance. My deep gratitude goes to Dr. Hiba Badreldin Khalil ,Who spent most of her time directing and guiding me.

Also I would like to thanks all staff in Omdurman military hospital, special thanks to Dr .Nazik Abd Almahmmod for her encouragement and advice .

I would like to express my deep graduate and thanks to everyone who help me throughout this work at any step of it, a special thanks to my friends Omyma Abdelrahim and Alhaj Nour Eldin and May Mohmmed Ali, Thanks extend to all people whom the blood sample has been collected from. To all of them thanks with regards.

Abstract

Background; Thyroid disorders represent an important public health problem worldwide ranking second to diabetes as the commonest endocrinological disorder seen in adult medical practice and presenting a myriad of devastating consequences if not treated early. This study aimed to estimate the D-dimer levels in hyperthyroidism and hypothyroidism female under treatment.

Materials and Methods; A descriptive cross sectional study obtained at Omdurman Military hospital and Asia Hospital during the period of (February - July 2017), the practical done in Omdurman Military Hospital. 4.5 ml of venous blood collected from 60 thyroid dysfunction volunteers placed in 3.2% tri sodium citrate container then centrifuge to get platelet poor plasma (PPP).D-dimer was estimated using Ichroma™ D-Dimer and all data was analyzed by SPSS version 11.5.

Results; . The mean of D-dimer in hypothyroidism 280ng/ml and mean of D-dimer in hyperthyroidism 246ng/ml.

The study showed that no significant difference in D-dimer in hypothyroidism and hyperthyroidism volunteers (p.*value*=0.4) and no correlate between D-dimer and TSH, T4 and T3 in both study group (P. *values* 0.66, 0.92 and 0.89) respectively.

The result showed that weak positive correlation between D-dimer and age group in hypothyroidism patients (p.value= 0.01, r= 0.43) and hyperthyroidism patients (p.value= 0.02, r= 0.41), also there was no significant difference in D-dimer according to BMI and duration time of disease in hypothyroidism patients (p. *value* ,0.7 and 0.5) and hyperthyroidism patients (p. *value* ,0.7and 0.9) respectively.

Conclusion; Sudanese female with thyroid dysfunction presented normal D-dimer.

مستخلص البحث

مقدمة البحث :تعتبر اضرابات الغدة الدرقية من اهم المشاكل الصحية والعامة في جميع انحاء العالم، وتحتل المرتبة الثانية بعد امراض السكري ويعتبر اضطراب الغدد الصم الاكثر شهرة في الممارسات الطبية ويأتي بعدد لا يحصي من العواقب المدمره آذا لم يعالج. هدفت هذه الدراسة الي قياس معدل دي دايمر عند السيدات اللأتي يعانين من ضمور او زيادة في إفراز الغدة الدرقية أثناء العلاج.

الطرق و الوسائل :هي دراسة وصفية مقطعية اجريت في مستشفي السلاح الطبي امدرمان ومستشفي آسيا في الفترة من فبراير وحتى يوليو 2017 ,أجري العملي بمستشفي السلاح الطبي في امدرمان ،أخذ ٤.٥ مليلتر من الدم الوريدي من60 متبرعين مرضي بالغدة الدرقية ووضع في وعاء يحتوي على مانع تجلط ثلاثي سترات الصوديوم واستخلص المصل الدموي،قيس اختبار دي دايمر بواسطة جهاز اي كروما تي ام، وحللت النتائج بواسطة برنامج الحزم الاحصائية للعلوم الاجتماعية الأصدار 11.5.

نتائج الدراسة: .متوسط معدل دي دايمر في المرضي الذين يعانون من ضمور الغدة الدرقية 280نانوجرام/مليلتر وفي المرضي الذين يعانون من فرط افراز الغدة الدرقية 246 نانوجرام /مليلتر .

لا توجد اختلافات ذات دلالة إحصائية في متوسط دي دايمر عند مرضي قصور الغدة الدرقية وفرط افراز الغدة الغدة الدرقية بقيمة معنوية (0.4) ،ولا توجد علاقة بين الدي دايمر و, الثايروكسين هرمون محفز الغدة الدرقية اوثلاثي ايودو ثايرونين و الثايروكسين الرباعي بقيمة معنوية (0.89 ,0.92 ,0.66) بالتتابع.

أوضحت النتائج وجود علاقة ايجابية ذات دلالة احصائية عند مقارنة دي دايمر مع عمر المريض في مرضي قصور الغدة الدرقية بقيمة معنوية (0.01)و بقيمة معنوية (0.02) عند مرضي فرط نشاط الغدة الدرقية، أيضآ لا توجد اختلافات ذات دلالة إحصائية في متوسط دي دايمر حسب نسبة طول المريض الي وزنة أو مدة المرض في مرضي قصور الغدة الدرقية بقيمة معنوية (0.7 و0.5)،وعند مرضي فرط افراز الغدة الدرقية بقيمة معنوية (0.7 و0.9) بالتتابع.

الخلاصة: خلصت الدراسة الي ان معدل الدي دايمر طبيعي في السيدات السودانيات اللآتي يعانين من اضطرابات الغدد الصم .

List of contents

List of Tables

List of Figures:

Abbreviations

APC	Activated protein C
BMI	Body mass index
CBC	Complete blood count
CHO	Coronary heart disease
CRP	C - reactive protein
DIC	Disseminated intravascular coagulation.
DVT	Deep venous thrombosis
EDTA	Ethylene diamine tetra acetic acid
ESR	Erythrocyte sedimentation rate
FDPs	Fibrin degradation products
FEU	Fibrinogen equival unit
GP	Glycoprotein
GPV	Glycoprotein 5.
HMWK	High molecular weight kininogen
HT	Hashimoto's Thyroiditis
MPV	Mean platelet volume
PAI	Plasminogen activator inhibitor
PBS	Phosphate buffer saline.
PE	Pulmonary embolism.
PPP	Platelet poor plasma
PPT	Postpartum thyroiditis.
RNA	Ribonucleic acid
S H	Subclinical hypothyroidism
SPSS	Statistical package for social science.

Tg	Thyroglobulin
T.PA	Tissue plasminogen activator.
T3	Tri-iodothyronine
T4	Thyroxine
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor.
TFTs	Thyroid function tests
TPO	Thyroid peroxidase
TRH	Thyroid regulating hormone
TSH	Thyroid stimulating hormone
USI	Universal salt iodization.
VWF	Von Willebrand factor

Chapter One

Introduction and Literature Review

Chapter One

1. Introduction and Literature Review

1. 1 Thyroid dysfunction

Thyroid disorders represent an important public health problem worldwide ranking second to diabetes as the commonest endocrinological disorder seen in adult medical practice and presenting a myriad of devastating consequences if not treated early (Vanderpump, 2011). Epidemiology and clinical features of thyroid disease are determined by the supply of iodine, an essential element in the synthesis of thyroid hormones (Zimmermann *et al.*, 2008). Additionally, the presence of both excess and deficient iodine levels can pose adverse health effects (Brotfain *et al*., 2013). Chronic iodine deficiency results in goiter formation and, if severe, hypothyroidism, this can result in severe implications including cretinism, intellectual impairments, increased pregnancy loss, and infant mortality (Black *et al*., 2008).

Sub-Saharan Africa has for a long-time been classified as an area of moderate to severe iodine deficiency (Zimmermann,2013).

The symptoms of thyroid disease vary depending on the type. There are four general types: first is hypothyroidism (low function) caused by not having enough thyroid hormones, second is hyperthyroidism (high function) caused by having too much thyroid hormones, third structural abnormalities, most commonly an enlargement of the thyroid gland(tumors which can be benign or cancerous), 4)abnormal thyroid function tests without any clinical symptoms(Bauer, 2013).

1.1.1 Hypothyroidism

Define as a low free T4 level with a normal or high level of TSH it is caused by sub optimal circulating concentration of thyroid hormone, it becomes more prevalent with age, affecting about 6%of people over 60 years and more common in women and if the hormone deficiency is caused by primary disorder of thyroid gland the patient may present weigh gain, myopathy, menstrual disturbance and constipation (Bishop and Edward**,** 2010).

There are three type of hypothyroidism: primary, secondary and tertiary; In primary hypothyroidism the thyroid itself the source of problem while in secondary the pituitary gland not stimulating thyroid gland to produce enough hormone the same is true with tertiary hypothyroidism the hypothalamus does not produce TRH which plays an important role in stimulating the pituitary gland to produce TSH (Holm, 2012).

Hypothyroidism has been associated with various abnormalities of the coagulation system. These modifications involve both primary and secondary homeostasis, and may range from minor subclinical alterations to significant clinical disturbances (Manfredi *et al*.,2008), increased fibrinolytic activity is reported in some patients with severe hypothyroidism, a hypercoagulable state in patient with moderate/ mild hypothyroidism has been reported (Akinci *et al*.,2011). Subclinical hypothyroidism (SH) is associated with an abnormally high risk of cardiovascular and cerebrovascular disease (Jabbar and Razvi, 2014).

1.1.1.1 Incidence of hypothyroidism

The total prevalence of goitre reported in sundaes studies from 1980s to 1990s ranged from 13% in the eastern city of Port Sudan and 17% in Khartoum state, to 78% in the central region and 87% in Darfur (Abdel Monim *et al*., 2010). In the west, according to a national study conducted in 1997, the overall prevalence of all

types of goitre was 22% and prevalence figures ranged from 5% in the city of Khartoum to 42% in the Upper Nile region. It has been estimated that every year more than 200 000 children born in the Sudan are at risk of iodine deficiency and that 3% of those children may develop cretinism, while 10% may experience severe intellectual impairment and 87% less severe intellectual disability (Abdel Monim et *al*., 2010).

1.1.1.2 Prevalence of hypothyroidism

Hypothyroidism is more prevalent in women who have a four to ten times greater than men. It can be present at birth, but has a higher occurrence rate between the ages of 30 and 60 years. It occurs in close to 10% of women and 6% of men over the age of 65years. Primary Hypothyroidism is more common than secondary with approximately 95% of all people diagnosed categorized as the primary type (Goodman and Fuller, 2009).

1.1.1.3 Etiology of hypothyroidism

Iodine deficiency is the most common cause of primary hypothyroidism and endemic goiter worldwide. In areas of the world with sufficient dietary iodine, hypothyroidism is most commonly caused by the autoimmune disease Hashimoto's thyroiditis (chronic autoimmune thyroiditis). Hashimoto's may be associated with a goiter. It is characterized by infiltration of the thyroid gland with T lymphocytes and auto antibodies against specific thyroid antigens such as thyroid peroxidase, tyro globulin and the TSH receptor (Chakera *et al*., 2012).

Primary Hypothyroidism may also be caused by radiation treatment or surgical removal of thyroid. This may be present in people treated for goiters, Hyperthyroidism , Hodgkin’s disease, lymphoma, Grave’s disease or cancer of the Head, neck, or thyroid gland (Chakera *et al*., 2012).

Rarely, primary hypothyroidism is congenital, or present at birth, or caused by deficient iodine intake in the diet. Secondary Hypothyroidism is caused by pathology to the pituitary gland or Hypothalamic disease which causes under stimulation to the thyroid gland secondary to inadequate amounts of TSH released to be utilized to make the thyroid hormone (Goodman and Fuller, 2009).

1.1.1.4 Signs and Symptoms of hypothyroidism

People with hypothyroidism often have no or only mild symptoms. Numerous symptoms and signs are associated with hypothyroidism, and can be related to the underlying cause, or a direct effect of having not enough thyroid hormones. Hashimoto's thyroiditis may present with the mass effect of a goiter (Longo *et al.*, 2011).

Table (1-1): Signs and Symptoms of hypothyroidism (Longo *et al.*, 2011).

Symptoms	**Signs**
Fatigue	Dry ,coarse skin
Feeling cold	Cool extremities
Poor memory and concentration	Myxedema (muco polysaccharide deposits in the skin)
Weight gain with poor appetite	Hair loss
Shortness of breath	Slow pulse rate
Hoarse voice	Swelling of the limbs
In females, heavy menstrual periods (and later light periods)	Delayed relaxation of tendon reflexes
Abnormal sensation	Carpal tunnel syndrome

1.1.1.5 Myxedema coma

Myxedema coma is a rare but life-threatening state of extreme hypothyroidism. It may occur in those who are known to have hypothyroidism when they develop another illness, but it can be the first presentation of hypothyroidism, there may be physical signs suggestive of hypothyroidism, such as skin changes or enlargement of the tongue (Klubo *et al*., 2012).

Mechanical ventilation may be required, as well as fluid replacement, vasopressor agents, careful re warming, and corticosteroids (for possible adrenal insufficiency which can occur together with hypothyroidism). Careful correction of low sodium levels may be achieved with hypertonic saline solutions or vasopressin receptor antagonists (Klubo *et al*., 2012).

1.1.1.6 Hashimoto's thyroiditis

Hashimoto's thyroiditis (HT) is the most prevalent autoimmune thyroid disorder. Intrathyroidal lymphocytic infiltration is followed by a gradual destruction of the thyroid gland which may lead to subclinical or overt hypothyroidism, biochemical markers of the disease are thyroid peroxidase and/or thyroglobulin autoantibodies in the serum which are present with a higher prevalence in females than in males and increase with age, although exact mechanisms of aetiology and pathogenesis of the disorder are not completely understood, a strong genetic susceptibility to the disease has been confirmed predominantly by family and twin studies. Several genes were shown to be associated with the disease occurrence, progression, and severity (Zaletel and Gaberšček, 2011).

Hypothyroidism may not be present until later in life and affects women more than men. Often times, hypothyroidism is ignored or misdiagnosed due to the multiple symptoms that appear similar to other diseases (Gaitonde *et al*., 2012).

In general, these symptoms are due to the decreased production of thyroid hormone. Most of the symptoms are not manifested in the early stages of the disease. When the metabolic rate drops to a critical level, a life threatening emergency known as "Myxedema Coma" can occur. This event is characterized by hypothermia, hypoglycemia, severe bradycardia and altered level of consciousness (Hampton, 2013).

HT is characterized by the loss of thyroid follicular cells, and the presence of auto antibodies against tissue-specific antigens such as thyroid peroxidase (TPO) and thyroglobulin (Tg). The lymph system of the thyroid gland becomes involved and this leads to the death of the thyrocytes with the end result of hypothyroidism and Hashimoto's Thyroiditis (Glick *et al*., 2013).

1.1.1.7 Diagnosis of hypothyroidism

Number of tests that can be used to test the function of the thyroid, for the presence of diseases, and for the success or failure of treatment. Blood tests in general aim to determine the cause of thyroid dysfunction. Thyroid function tests include a battery of blood tests including the measurement of the thyroid hormones T3 and T4, as well as the measurement of TSH (David and Dolores, 2011).

Table (1.2): diagnosis of hypothyroidism (David and Dolores , 2011).

TSH	T4	Interpretation
Normal	Normal	Normal thyroid function
Elevated	Low	Overt hypothyroidism
Normal/low	Low	Central hypothyroidism
Elevated	Normal	Subclinical hypothyroidism

Ultrasound of the thyroid may be used to reveal whether structures are solid or filled with fluid, helping to differentiate between nodules and goiters and cysts. It

may also help differentiate between malignant and benign lesions, fine needle aspiration biopsy may be taken concurrently of thyroid tissue to determine the nature of a lesion (David and Dolores , 2011).

1.1.1.8 Prevention of hypothyroidism

Hypothyroidism may be prevented in a population by adding iodine to commonly used foods. This public health measure has eliminated endemic childhood hypothyroidism in countries where it was once common. In addition to promoting the consumption of iodine-rich foods such as dairy and fish, many countries with moderate iodine deficiency have implemented universal salt iodization (USI) (Charlton and Skeaff , 2011).

1.1.1.9 Management of hypothyroidism

Most people with hypothyroidism symptoms and confirmed thyroxine deficiency are treated with a synthetic long-acting form of thyroxine, known as levothyroxine (thyroxine). In young and otherwise healthy people with overt hypothyroidism, a full replacement dose (adjusted by weight) can be started immediately; in the elderly and people with heart disease a lower starting dose is recommended to prevent over supplementation and risk of complications Lower doses may be sufficient in those with subclinical hypothyroidism, while people with central hypothyroidism may require a higher than average dose (Garber *et al*., 2012).

1.1.2 Hyperthyroidism

Excessive production of the thyroid hormones is called hyperthyroidism, which is most commonly a result of Graves' disease, a toxic multinodular goitre, a solitary thyroid adenoma, or inflammation. Other causes include drug-induced excess of iodine, particularly from amiodarone, an antiarrhythmic medication; an excess caused by the preferential uptake of iodine by the thyroid following iodinated

contrast imaging; or from pituitary adenomas which may cause an overproduction of thyroid stimulating hormone(Nicki *et al.*, 2010).

Is a constellation of finding that result when peripheral tissues are presented with and respond to an excess of thyroid hormones. Thyrotoxicosis can be result of excessive thyroid hormones ingestion, leakage of thyroid stored hormone from the storage in thyroid follicles or excessive production of thyroid hormones (hyperthyroidism),the manifestations of thyrotoxicosis vary depending on the degree of thyroid hormone elevation and status of affected individual. Symptoms of disease include anxiety, emotional lability, weakness, tremor, palpitation, increase perspiration, heat intolerance and weight loss despite abnormal or increased appetite (Bishop and Edward**,** 2010).

It is associated with a hyper coagulable state, several coagulation and fibrinolytic parameters appear to be affected by thyrotoxicosis; elevated plasma levels of factor VIII (FVIII), factor IX (FIX), vonWillebrand factor (VWF), and fibrinogen, and a reduced fibrinolytic activity due to increased levels of plasminogen activator inhibitor-1 (PAI-1) have been reported in both hyperthyroid patients and healthy subjects after taking thyroid hormones (van Zaane *et al.*, 2011).

1.1.2.1 Incidence of the disease

Thyrotoxicosis due to toxic nodular goitre is more common in people aged over 60 years. Thyroiditis, in which destruction of thyroid cells causes release of thyroid hormones into the circulation, is implicated in about 10% of thyrotoxicosis cases. Other causes include exogenous thyroid hormone excess, drug-induced hyperthyroidism, TSH-secreting pituitary adenomas and pituitary resistance to thyroid hormones, thyrotoxicosis is still under-diagnosed however - it has been shown that in people older than 65 years, undiagnosed hyperthyroidism occurs in 0.3% of people and around 2% of people aged over 65 years have subclinical hyperthyroidism (Franklyn and Boelaert, 2012).

1.1.2.2 Risk factors of hyperthyroidism

Family history, high iodine intake, smoking (particularly for thyroid-associated ophthalmopathy), trauma to the thyroid gland (including surgery) and Toxic multinodular goitre (which is especially associated with an increased Iodine intake, either from a change in diet or an acute dose from iodine containing agents (amiodarone, contrast agents) (Franklyn and Boelaert, 2012).

1.1.2.3 Etiology of hyperthyroidism

1.1.2.3.1 Graves' disease

Graves' disease is an autoimmune disorder that is the most common cause of hyperthyroidism. In Graves' disease, for an unknown reason auto antibodies develop against the thyroid stimulating hormone receptor. These antibodies activate the receptor, leading to development of agoitre and symptoms of hyperthyroidism, such as heat intolerance, weight loss, diarrhea and palpitations. Occasionally such antibodies block but do not activate the receptor, leading to symptoms associated with hypothyroidism (Smith *et al.*,2016).

In addition, gradual protrusion of the eyes may occur, called Graves' ophthalmopathy, as may swell of the front of the shins. Graves' disease can be diagnosed by the presence of pathomnomonic features such as involvement of the eyes and shins, or isolation of auto antibodies, or by results of a radio labelled uptake scan, and can treated with anti-thyroid drugs such as propylthiouracil, which decrease the production of thyroid hormones, surgical removal of the gland with subsequent thyroid hormone replacement may be considered (Smith *et al.*,2016).

1.1.2.3.2 Toxic thyroid adenoma

The most common etiology in Switzerland, 53%, thought to be atypical due to a low level of dietary iodine in this country (Andersson *et al.*, 2010).

1.1.2.4 Signs and Symptoms of hyperthyroidism:

Table (1-3): signs and symptoms of hyperthyroidism (Chang *et al.*, 2014).

Symptoms	Signs
Weight loss despite an increased appetite	Palmar erythema.
Weight gain.	Sweaty and warm palms.
Increased or decrease appetite.	Fine tremor.
Irritability.	Tachycardia - may be atrial fibrillation
Weakness and fatigue.	Hair thinning or diffuse alopecia.
Diarrhoea ± steatorrhoea.	Urticaria, pruritus.
Sweating.	Brisk reflexes.
Tremor.	Goitre.
Mental illness: may range from anxiety to psychosis.	Proximal myopathy (muscle weakness ±wasting).
Heat intolerance.	Gynaecomastia.
Loss of libido.	Lid lag (may be present in any cause of hyperthyroidism).
Oligomenorrhoea or Amenorrhoea .	heart failure (common in the elderly).

Although these symptoms may be present, the symptoms and signs can be variable and in some patients they are very mild. Thyrotoxic periodic paralysis is a serious complication characterized by muscle Paralysis and hypokalaemia due to a massive intracellular shift of potassium. An annual incidence of up to 2% has been reported in Asian people with thyrotoxicosis (Chang *et al.*, 2014).

1.1.2.5 Thyrotoxic crisis or storm

Patients may rarely present with Thyrotoxic crisis or storm in either previously undiagnosed or ineffectively treated cases. A thyroid storm is a rare condition affecting 1-2% of patients with hyperthyroidism (Nakashima *et al*., 2014).

The typical symptoms of thyroid storm are hyperthermia and mental disturbance, along with thyrotoxic symptoms. It is associated with precipitating events, such as the withdrawal of an anti-thyroid drug, radio-iodine therapy, infection and surgery. Management is with intravenous fluids, beta-blockers, anti-thyroid drugs and steroids, it is also important to look for the presence of Addison's disease in these patients, it has 20-30% mortality due to arrhythmias and hypothermia (Akamizu *et al*., 2012).

1.1.2.6 Diagnosis of hyperthyroidism

1.1.2.6.1 Thyroid stimulating hormone

TSH which has the highest sensitivity and specificity for hyperthyroidism, and then subsequently obtain free thyroxine (T_4) and total triiodothyronine (T_3) levels) if the TSH level is low. Others prefer to order all three tests if hyperthyroidism is suspected to make the diagnosis more efficiently. Many laboratories perform reflex free T_4 testing if TSH is suppressed (Van Deventer *et al*.,2011).

1.1.2.6.2 Auto antibodies

These are most commonly seen in Graves' disease:

Anti microsomal antibodies against thyroid peroxidase. Thyroid peroxidase antibodies are present in about 75% of cases of Graves' hyperthyroidism and can help to differentiate autoimmune disease from toxic nodular hyperthyroidism (Franklyn and Boelaert, 2012).

1.1.2.6.3 Anti thyroglobulin antibodies

Recent years have brought significant technical advances in the ability to reliably test for TRAb in Graves' patients. This has resulted in the rise of the TRAb test to the performance characteristics required for routine use in clinical practice, novel TR Ab tests are now adequate for a reliable and inexpensive diagnosis of Graves disease (Barbesin and Tomer, 2013).

1.1.2.7 Management of hyperthyroidism

1.1.2.7.1 Anti-thyroid drugs

Carbimazole (methimazole) or propylthiouracil, these drugs act very quickly and inhibit the production of thyroid hormones, and full benefit may take 2-3 weeks to become apparent. The recommended starting dose of Carbimazole or methimazole is 10-20 mg per Day (Franklyn and Boelaert, 2012).

1.1.2.7.2 Radio iodine

Radioactive iodine is given to the patient as a drink and is taken up by the thyroid gland, leading to destruction of the gland. It can take 3-4 months to take effect, anti-thyroid drugs should be stopped 5-7 days before treatment with radioiodine because continuous use reduces thyroid iodide uptake and retention, which in turn reduces cure rates, It cannot be given to pregnant or breast-feeding females and females must be advised not to get pregnant for at least six months.Radioactive iodine may also worsen eye disease in Graves' thyrotoxicosis; this is more marked in smokers (Franklyn and Boelaert, 2012).

1.1.2.7.3 Thyroidectomy

This treatment option is preferred in patients with goiter-induced compressive symptoms and in patients with contraindications to radioactive iodine ablation or thionamides. Besides general anesthesia risk, thyroidectomy carries a risk of inadvertently injuring parathyroid glands and recurrent laryngeal nerves (Randolph *et al.,* 2011).

1.1.2.8 Prognosis of hyperthyroidism

Hyperthyroidism is characterized by relapses and remittances.

Surgical treatment and radioactive iodine can both lead to hypothyroidism and

Thus close follow-up with TFTs is required.

Spontaneous remission is seen in <10% and may not persist.

There is an increased risk of

- Death from osteoporotic fracture (Mirza and Canalis, 2015).
- Death from cardiovascular disease and stroke (independent of a trial fibrillation) in untreated hyperthyroidism (Tsai *et al.,* 2015).

1.2 Hemostasis

Hemostasis is the term used to describe the arrest of bleeding or the interruption of blood flow through a vessel, it is represents an intricate, highly balanced interaction between blood vessels, platelets, plasma coagulation factors and fibrinolytic proteins in the formation and dissolution of blood clots, under normal conditions these balanced maintain blood in a free flowing state (Malcolm, 2013).It may be categorized into primary (platelet plug formation), secondary (formation of a stabilized fibrin clot through the coagulation cascade) and tertiary (formation of plasmin for breakdown of fibrin via fibrinolysis) concurrent processes, disorders of hemostasis or unbalanced hemostasis may lead to hypo coagulation (hemorrhage) or hyper coagulation (thromboembolic disorders) (Malcolm, 2013).

It is occurs when blood is present outside of the body or blood vessels. It is the instinctive response for the body to stop bleeding and loss of blood. during hemostasis three steps occur in a rapid sequence, vascular spasm is the first response as the blood vessels constrict to allow less blood to be lost. In the second step, platelets plug formation, platelets stick together to form a temporary seal to cover the break in the vessel wall. The third and last step is called coagulation or blood clotting. Coagulation reinforces the platelet plug with fibrin threads that act as a "molecular glue"(Marieb *et al*., 2010)

The hemostatic system consists of blood vessels, platelets, and the plasma coagulation system including the fibrinolytic factors and their inhibitors, when a blood vessel is injured, three mechanisms operate locally at the site of injury to control bleeding and essential for normal hemostasis: (1) vessel wall contraction, (2) platelet adhesion and aggregation (platelet plug formation), and (3) plasmatic coagulation to form a fibrin clot, all three mechanisms are essential for normal hemostasis (Munker *et al*.,2007).

1.2.1 Vascular system

It is prevents bleeding through vessel contraction, diversion of blood flow from damaged vessels, initiation of contact activation of platelets with aggregation, and contact activation of the coagulation system, the vessel wall contains varying amounts of fibrous tissue such as collagen and elastin, as well as smooth muscle cells and fibroblasts. Arteries are the vessels that take blood away from the heart and have the thickest walls of the vascular system,Veins return blood to the heart, and are larger with a more irregular lumen than the arteries however, are thin walled, with elastic fibers found only in larger veins, arterioles are a smaller subdivision of arteries, and venules are smaller subdivisions of veins, capillaries are the thinnest walled and most numerous of the blood vessels, (Ciesla, 2007).

1.2.2 The Endothelium

The endothelium actively affects the function of all Hemostasis components. The endothelium has two roles: activation and inhibition of Hemostasis (Baklaja *et al*., 2008).

Endothelial cells line the vessel walls of arteries, veins, and microvessels. The local shear stress, blood oxygenation, and smooth muscle cell content vary between these vessels and consequently the endothelial cells in the various vascular beds respond differentially to procoagulant signaling. Endothelial cells are dynamic and adapt their phenotype according to the nature of the local milieu (Pober and Sessa, 2007) .For example, vascular shear stress can influence the coagulant potential of endothelial cells. Arterial shear stress can induce the transcription factors Kruppel Like Factor (KLF) 2 and KLF 4 and attenuate coagulation in atherosclerosis-poor regions, but has no effect in atherosclerosis-prone areas with disturbed blood flow (Pober and Sessa, 2007).

1.2.3 Platelets

platelets are the cellular effectors of hemostasis in mammals. They also play important roles in physiologic processes such as wound healing and inflammatory/immune responses, and in pathological developments including atherosclerosis and tumor metastasis. Postnatal platelet production is centered on the bone marrow, where mature megakaryocytes (MKs) move to sinusoids and extend long processes (proplatelets) that shed platelets into the bloodstream (Machlus and Italiano, 2013).

Megakaryocyte and platelet production is regulated by thrombopoietin, a hormone produced in the kidneys and liver. Each megakaryocyte produces between 1,000 and 3,000 platelets during its lifetime. An average of 1011 platelets are produced

daily in a healthy adult. Reserve platelets are stored in the spleen, and are released when needed by splenic contraction induced by the sympathetic nervous system.
The average life span of circulating platelets is 8 to 9 days. Life span of individual platelets is controlled by the internal apoptotic regulating pathway, which has a Bcl-xLtimer (Mason *et al*.,2007).

1.2.3.1 Platelets adhesion

following blood vessel injury, platelets adhere to the exposed subendothelial matrix via specific glycoprotein (GP). Under condition of high shear, e.g. arterioles, the exposed subendothelial matrix is initially coated with VWF multimeres (Hoffbrand *et al*., 2006) . The platelets then make contact with VWF via the GPTh-XI-V complex on platelets, this itutiates platelet rolling in the direction of blood flow over the exposed VWF with activation of GPITh/IlIa receptors. Firm adhesion is established by the slower but stronger interaction of other glycoproteins including activated GPITh/IlIa with VWF and GPVI and integrin α1/ β2 with collagen and other component of the subendothelial matrix. Under static or low shear conditions, platelets adhere predominantly to collagen of the subendothelium. Collagen bind initially to GPIa/IIa, cross-links many of these integrin molecules, and in this way activates platelets (Hoffbrand *et al*., 2006).

1.2.3.2 Platelets activation

Activation of platelets is critical for aggregation. In particular the integrins, αIIbβ3, α2β1 and αvβ3 are normally present on the platelet surface in an inactive form, but platelet activation induces a conformational transition in these receptors that exposes ligand binding sites (Xiao *et al.*, 2004). αIIbβ3 is arguably the most important of these receptors as it is present at the highest density on the platelet surface. In addition, αIIbβ3 binds to multiple ligands that promote platelet-platelet

aggregation. These include fibrinogen, VWF, collagen, fibronectin and vitronectin (Varga-Szabo*et al*., 2008)

1.2.4 The Role of Platelets in Hemostasis

Two potent platelet aggregating agents are thrombin, which binds to Glycoprotein 5 (GPV) as well as to GPIb (vWF receptor), and collagen, which binds to GPIa/IIa. Thrombin and collagen can induce aggregation of platelets and secretion of platelet granular contents even if prostaglandin synthesis is blocked. A bond forms between fibrinogen and platelets through the interaction with platelet receptor complex GPIIb/IIIa. Fibrinogen binding only occurs after the platelet-activation-induced conformational change of the complex (Baklaja *et al*., 2008). GPIIb/IIIa is a transmembrane complex associated with actin on the inner surface of the platelet. Actin is a major component of platelet cytoskeleton. An actin-GPIIb/IIIa association is essential for clot retraction. Patients who show either the rare condition of a fibrinogenemia or lack GPIIb/IIIacomple(Glanzmannthrombastenia) have poor clot retraction and hemorrhagic syndrome (Baklaja *et al*., 2008).

1.2.5 Secondary Hemostasis

Secondary hemostasis consists of the cascade of coagulation serine proteases that culminates in cleavage of soluble fibrinogen by thrombin ,Thrombin cleavage generates insoluble fibrin that forms a crosslinked fibrin mesh at the site of an injury. Fibrin generation occurs simultaneously to platelet aggregation (Furie , 2009).

1.2.5.1 Tissue factor pathway (extrinsic)

The main role of the tissue factor pathway is to generate a "thrombin burst", a process by which thrombin, the most important constituent of the coagulation cascade in terms of its feedback activation roles, is released very rapidly, FVIIa

circulates in a higher amount than any other activated coagulation factor and leaves the circulation and comes into contact with tissue factor (TF) forming an activated complex (TF-FVIIa), then TF-FVIIa activates FIX and FX, the FXa and its co-factor FVa form the prothrombinase complex, which activates prothrombin to thrombin, it is then activates other components of the coagulation cascade, including FV and FVIII (which forms a complex with FIX), and activates and releases FVIII from being bound to vWF, FVIIIa is the co-factor of FIXa, and together they form the "tenase" complex, which activates FX; and so the cycle continues. ("Tenase" is a contraction of "ten" and the suffix "-ase" used for enzymes.) (Pallister and Watson ,2010).

1.2.5.2 Contact activation pathway (intrinsic)

The contact activation pathway begins with formation of the primary complex on collagen by high-molecular-weight kininogen (HMWK), prekallikrein, and FXII (Hageman factor). Prekallikrein is converted to kallikrein and FXII becomes FXIIa. FXIIa converts FXI into FXIa. Factor XIa activates FIX, which with its co-factor FVIIIa form the tenase complex, which activates FX to FXa. The minor role that the contact activation pathway has in initiating clot formation can be illustrated by the fact that patients with severe deficiencies of FXII, HMWK, and prekallikrein do not have a bleeding disorder. Instead, contact activation system seems to be more involved in inflammation, Despite this, interference with the pathway may confer protection against thrombosis without a significant bleeding risk (Long *et al*., 2015).

1.2.5.3 Final common pathway

Activated factor X along with its cofactor (factor V), tissue phospholipids, platelet phospholipids and calcium forms the prothrombinase complex which converts prothrombin to thrombin. This thrombin further cleaves circulating fibrinogen to

insoluble fibrin and activates factor XIII, which covalently crosslinks fibrin polymers incorporated in the platelet plug. This creates a fibrin network which stabilises the clot and forms a definitive secondary haemostatic plug (Hall, 2010).

1.2.6 Inhibition of coagulation

Several factors support haemostasis by inhibition, limiting blood coagulation to the injured vessels and preventing thromboembolic complications. The most important inhibitors are antithrombin and protein C, including its cofactor protein S. Antithrombin has important properties, including inhibition of coagulation and anti-inflammatory activity, together with heparin sulphate and other glucosaminoglycans *in vivo,* and with heparin during treatment, antithrombin blocks thrombin and activated factors that circulate freely in blood vessels, this prevents coagulation in non-injured blood vessels and limits thrombin activation to the location of the injury, protein C activates when free thrombin binds to thrombomodulin, an endothelial cell receptor, activated protein C (APC) and its cofactor protein S inactivate FVa and FVIIIa, which subsequently inhibit the production of thrombin. APC also has other properties, including anti-inflammatory and barrier-protective effects (Karlsson, 2014).

1.2.7 Fibrinolysis

The final step of fibrinolysis is to dissolve the fibrin clot. Tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA)activate plasminogen to form plasmin. Plasminogen circulates freely in plasma, binding to fibrin on the clot. Activation results in local fibrinolytic activity adjacent to the clot. When fibrin dissolves, a number of different fragments form (e.g. D-dimers). Fibrinolysis inhibitors, e.g. plasminogen activator inhibitor 1 (PAI-1), plasminogen activator inhibitor 2 (PAI-2) and antiplasmin, provide protection from uncontrolled fibrinolysis. (Karlsson, 2014).

1.2.8 Thrombosis

Thrombosis is the formation of an occlusive clot within a blood vessel that reduces blood flow to distal tissue and organs and restricts the delivery of nutrients and oxygen, resulting in localized tissue and organ necrosis. Large occlusive clots (thrombi) can break off and embolize to form secondary thrombi in distal locations. The process of thrombosis followed by embolism is collectively termed thromboembolism and can culminate in a variety of local or chronic disorders(Mackman and Triggers, 2008). For example, acute arterial thrombosis is triggered upon the rupture of an atherosclerotic plaque, and is the predominant cause of myocardial infarctions (heart attacks) and strokes, similarly, venous thromboembolism can be triggered by disturbed blood flow, hypercoagulable conditions, such as procoagulant changes in the blood, or endothelial activation, and is the major cause of deep vein thrombosis and pulmonary embolism (Mackman and Triggers, 2008).

1.2.9 D-dimer

D-dimer (or D dimer) is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two D fragments of the fibrin protein joined by a cross-link, D-dimer concentration can determine by a blood test to help diagnose thrombosis, since its introduction in the 1990s, it has become an important test performed in patients with suspected thrombotic disorders, while a negative result practically rules out thrombosis, a positive result can indicate thrombosis but does not rule out other potential causes. Its main use, therefore, is to exclude thromboembolic disease where the probability is low. In addition, it is used in the diagnosis of the blood disorder disseminated intravascular coagulation (Adam *et al*., 2009).

D-dimer testing is of clinical use when there is a suspicion of deep venous thrombosis (DVT), pulmonary embolism (PE) or disseminated intravascular coagulation (DIC). It is under investigation in the diagnosis of aortic dissection (Suzuki *et al*., 2010).

1.2.9.1 False results

False positive readings can be due to Liver disease, high rheumatoid factor, inflammation, malignancy, trauma, pregnancy and recent surgery as well as advanced age (Kabrhel *et al.,* 2010).

False negative readings can occur if the sample is taken either too early after thrombus formation , if testing is delayed for several days, additionally the presence of anticoagulation can render the test negative because it prevents thrombus extension. The anticoagulation medications dabigatran and rivaroxaban decrease D-dimer levels but do not interfere with the D-dimer assay (Baglin *et al*., 2012).

1.3 Relation between thyroid disease and thrombosis

The link between the hemostatic system and thyroid diseases has been known since the beginning of the past century, the first clinical association was described in 1913, when Kaliebe reported an episode of cerebral veinthrombosis in a thyrotoxic patient (Squizzato *et al.,* 2005). Both thyroid dysfunction and autoimmunity may modify physiological processes of primary and secondary hemostasis and lead to bleeding or thrombosis. Idiopathic thrombocytopenic purpura, secondary antiphospholipid syndrome, or acquired hemophilia have been associated in individual cases with autoimmune thyroid disorders (Marongiu *et al.,* 2004). Apossible link between hyperthyroidism and increased thrombosis potential was described more than a century ago, the reported evidence proposing an increased arterial and venous thrombotic risk in thyrotoxicosis is more recent (Danescu *et al*.,

2009).The mechanisms accounting for coagulation abnormalities in hypothyroidism are not well established, Most abnormalities have been attributed to decreased synthesis or activity of clotting factors, including von Willebrand factor (VWF) and factor VIII (FVIII:C), or to decreased response to adrenergic stimulation (enhanced VWF release from endothelial cells) due to thyroid hormone deficiency(Stuijver *et al.,* 2012). While many studies suggest a trend towards a hypercoagulable state in thyrotoxicosis and a hypocoagulable state in hypothyroidism, many reports are inconclusive and most of them were assessed as low-to-medium methodological quality (Stuijver *et al.,* 2012). Free thyroxine (FT4) and thyroid-stimulating hormone (thyrotropin, TSH) levels are inversely related: when FT4 rises, TSH drops, and vice versa. Although it is generally assumed that FT4 levels are related to altered coagulation parameters, it remains unknown whether this effect on coagulation is partially mediated by TSH. Recently, more evidence has been provided showing that TSH can have a direct effect itself in peripheral tissues such as bone, adipose tissue and muscle, mediated via the TSH receptor (DeLloyd *et al.,* 2010).

1.4 Previous studies

In 2015, Lupoli *et al* were conclude that sub clinical hypothyroidism patients exhibit a prothrombotic status, which is reverted by a 6-month levothyroxine (L-T4) treatment(Lupoli et al. *et al*., 2015).

In 2014, Mazur *et al* were conclude that after 3months of thyroid function normalizing therapy, 32 (91.4%) hyperthyroid and 30 (85.7%) hypothyroid subjects achieved euthyroidism and had improved fibrin clot properties (all $p<0.05$).(Mazur *et al.,* 2014).

In 2012, Danka *et al* were found that thyrotoxicosis shifts the haemostatic balance towards a hypercoagulable and hypofibrinolytic state with a rise in factors VIII and IX, fibrinogen, D-dimer, von Willebrand factor, and plasminogen activator inhibitor-1, thus induce a prothrombotic state, which is therefore likely to be a risk factor for venous thrombosis (Danka *et al.,* 2012).

In 2011, Brona *et al* were found Hyperthyroidism is associated with a tendency toward hypercoagulation and hyperfibrinolysis. The changes observed in plasma fibrinogen and D-dimers levels are reversible after treated with radioiodine. Fibrinogen level decreases within reference range and D-dimer level decreases almost to the upper reference range.(Brona *et al*.,2011).

The mechanisms accounting for coagulation abnormalities in hypothyroidism are not well established. Most abnormalities have been attributed to decreased synthesis or activity of clotting factors, including von Willebrand factor (VWF) and factor VIII (FVIII:C), or to decreased response to adrenergic stimulation (enhanced VWF release from endothelial cells) due to thyroid hormone deficiency (Yango *et al*.,2011).

1.5 Rationale

Patients with thyroid abnormalities have various changes in the coagulation and fibrinolytic system, ranging from bleeding to thrombosis, the risk of thrombosis in subclinical and moderate hypothyroidism where as bleeding tendency in sever hypothyroidism. (Lupoli *et al.*, 2015). Hyperthyroidism is associated with hypercoagulability state and appear with elevated plasma levels of factor VIII (FVIII), factor IX (FIX), von Will brand factor (VWF) (Danka *et al.*, 2012). Defining the contribution of the hypercoagulable state to the pathophysiology of thyroid dysfunction requires more researches and further studies.

As far as you Know There was no available information regarding affect of thyroid disease treatment on D-dimer among Sudanese female.

1.6 Objectives

1.6.1 General objective

To estimate the levels of D-dimer among thyroid abnormalities Sudanese women's.

To estimate CBC among thyroid abnormalities Sudanese women's to exclude leukocytosis.

1.6.2 Specific objectives

1. To measure the levels of D-dimer in hypothyroidism and hyperthyroidism women.
2. To correlate the D- dimer level with duration time of disease ,age group and BMI.

Chapter Two

Material and Methods

Materials and Methods

2.1 Study design and duration

A descriptive cross-sectional study conducted in the period from February to July 2017.

2.2 Study population and area

The study was carried out in thyroid dysfunction female who attended to the out patients clinic at Omdurman military hospital and Asia hospital, Omdurman state.

2.3 Inclusion criteria

Sudanese womens suffering from thyroid abnormalities with normal CBC to exclude leukocytosis.

2.4 Exclusion criteria

Patients newly diagnosed thyroid dysfunction patients (hyperthyroidism or hypothyroidism) or had recent thrombosis, bleeding infection or inflammation or disease that is known to affect the parameters investigated, Obesity , women use contraceptive pills ,and patients had recent surgery.

2.5 Sample size

Sixty diagnosed thyroid dysfunction Sudanese female years were recruited to participate in this study.

2.6 Data collection

Data for thyroid functiontest and other parameters were collected with informed consent agreement; each female interviewed to complete a structured questionnaire, which included personal information on age, duration of disease, BMI and medical history of disease.

2.7 Methods

2.7.1 Sample collection

Seven point five ml of venous blood collected using sterile disposable plastic syringe after cleaning the vein puncture area with 70% ethanol **,** the sample was

divided in tow part,(2.5 ml) was added to EDTA using to analyze CBC to exclude leucocytosis the other (5 ml) was added to the anticoagulant at ratio of 4.5 to 5.0of citrate (3.2%(0.109M) buffered sodium citrate and gently mixed.

The sample was centrifuged at 1300 rpm for 15min to obtain platelet poor plasma (PPP) .the PPP placed into plastic tubes , capped and frozen at -70 used for D-dimer estimation after ethical informed consent and self –administrated per-coded questionnaire which was specifically designed to obtain information that helped in study.

2.7.2 Estimation of D-dimer

Principle

The test uses the sandwich immune detection method, such that the detection antibody in buffer binds to D-Dimer in the plasma sample and antigen-antibody complexes are captured by antibodies that have been immobilized on the test strip as sample mixture migrates through nitrocelluose matrix. The more D-Dimer antigen in the plasma, the more antigen-antibody complexes are accumulated on test strip. Signal intensity of fluorescence on detection antibody reflects amount of antigen captured and is processed by ichroma™ Reader to show D-Dimer concentration in the specimen. The working range of ichroma™ D-Dimer test is 50 – 10,000 ng/ml. * Reference Value: 500 ng/mL (FEU: Fibrinogen equivalent units).

Components and Reagents

Ichroma™ D-Dimer consists of Cartridge, an ID Chip, and Detection Buffers. - The test cartridge contains a test strip; on the membrane of which, antibodies against D-Dimer and streptavidin have been immobilized at the test line and the control line respectively.

- Each test cartridge is individually sealed in an aluminum foil pouch containing a desiccant. 25 sealed test cartridges are packed in a box which also contains an ID chip.
- The detection buffer pre-dispensed in a tube contains fluorochrome-labeled anti-D-Dimer antibodies, fluorescent labeled biotin-BSA, bovine serum albumin (BSA) as a stabilizer and sodium azide in phosphate buffered saline (PBS) as a preservative.
- The detection buffer is dispensed in each detection buffer tube. 25 detection buffer tubes are packed in a separate pouch which is further packed in a Styrofoam box provided with ice packs for the purpose of shipment.

Procedure

A 10 µl of plasma sample was added to a tube containing the detection buffer and then the lid was closed and mixed for 10 times. A 75 µl of a sample mixture was added to the test cartilage and Leaved at room temperature for 12 minutes and scanned by Ichroma reader. Ichroma reader calculated the result automatically and displayed D- dimer concentration of the test sample as ng/ml.

Reference value of Ichroma D-dimer is 500ng/ml.

Interpretation of the result

- Ichroma™ Reader calculates the test result automatically and displays D-Dimer concentration of the test sample as ng/mL.
- Working range of ichroma™ D-Dimer is 50-10,000 ng/mL.
- Reference value of ichroma™ D-Dimer is 500 ng/ml. (FEU: Fibrinogen equival units)**.**

2.8 Ethical considerations

The consent of the participants was taken (verbally and written) after being informed with all detailed objectives and benefits of the study with simple language.

2.9 Data analysis

The data were analyzed by using Statistical Package for Social Science (SPSS version 11.5) for windows version 7 using T- dependent test and personal correlation for testing significance difference on study group.

Continuous data was expressed as mean ± Standard Deviation and Categorical data was expressed in frequencies and percentages, the data presented in form of tables and graph. P *value* ≤ 0.05 was considered to be statistically significance

Chapter Three

Results

Chapter three

3 Results

3.1 Thyroid dysfunction frequency

Sixty thyroid dysfunction women were enrolled in this study and according to disease phenotype they classified in to 30 hypothyroidism and 30 hyperthyroidism.

There mean age was 42.83±13.49 in hypothyroidism and 37.90±STD 13.49 in hyperthyroidism.

3.2 Mean and std. deviation of D.dimer level among the hypothyroidism

Regard to correlation between D-dimer and age, duration of disease and BMI in hypothyroidism there was a significant correlation between D-dimer and age group P.*value* (0.01) and no correlation between D-dimer and duration time of disease and BMI (0.5, and 0.7) respectively ,The mean and Std.deviation of age, duration of disease and BMI in hypothyroidism patient(37.90 ±12.45, 5.87±5.08 ,24.52 ± 5.07)respectively, Table (3.1) .

Table (3.1) mean and Std. deviation of D.dimer in hypothyroidism

	Mean	Std. deviation	P.value
Age/years	42.83	13.49	0.01
Duration/years	11.90	9.77	0.5
BMI Kg/M2	27.40	4.37	0.7

3.3 Correlation between D-dimer and age in hypothyroidism patient

Standing correlation between D-dimer and age group showed that there was a weak positive correlation (p.value= 0.01, r= 0.4) Figure (3.1).

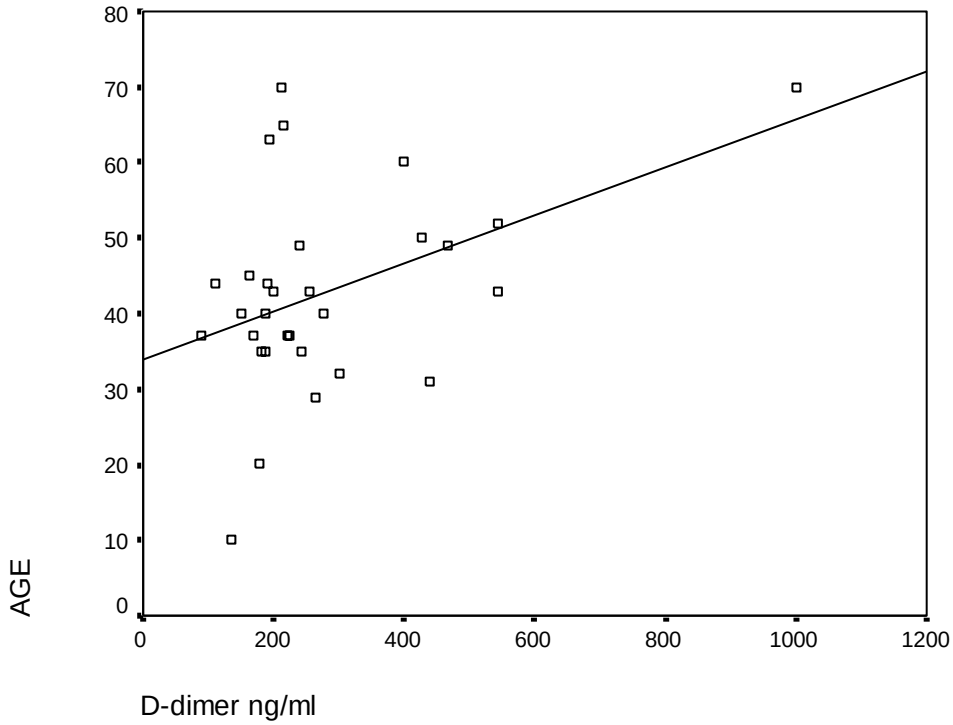


Figure (3.1): correlation between D-dimer and age group

Weak positive correlation (p.*value*= 0.01, r= 0.4)

3.4 Mean and std. deviation of D.dimer level among the hyperthyroidism

Regard to correlation between D-dimer and age, duration of disease and BMI in hyperthyroidism there was a significant correlation between D-dimer and age group P.*value* (0.02) and no correlation between D-dimer and duration time of disease and BMI (0.9, and 0.7) respectively, The mean and Std.deviation of age, duration of disease and BMI in hypothyroidism patients (37.90 ±12.45 ,5.87 ±5.08 ,24.52±5.07) respectively table (3.2).

Table (3.2)Mean and std. deviation and D.dimer level among the hyperthyroidism

	Mean	Std. deviation	P.value
Age/years	37.90	12.45	0.02
Duration/years	5.87	5.08	0.9
BMI Kg/M2	24.52	5.07	0.7

3.5 Correlation between D-dimer and age group in hyperthyroidism patient

Standing correlation between D-dimer and age group showed that there was a weak positive correlation (p.value= 0.02, r= 0.43) Figure (3.2).

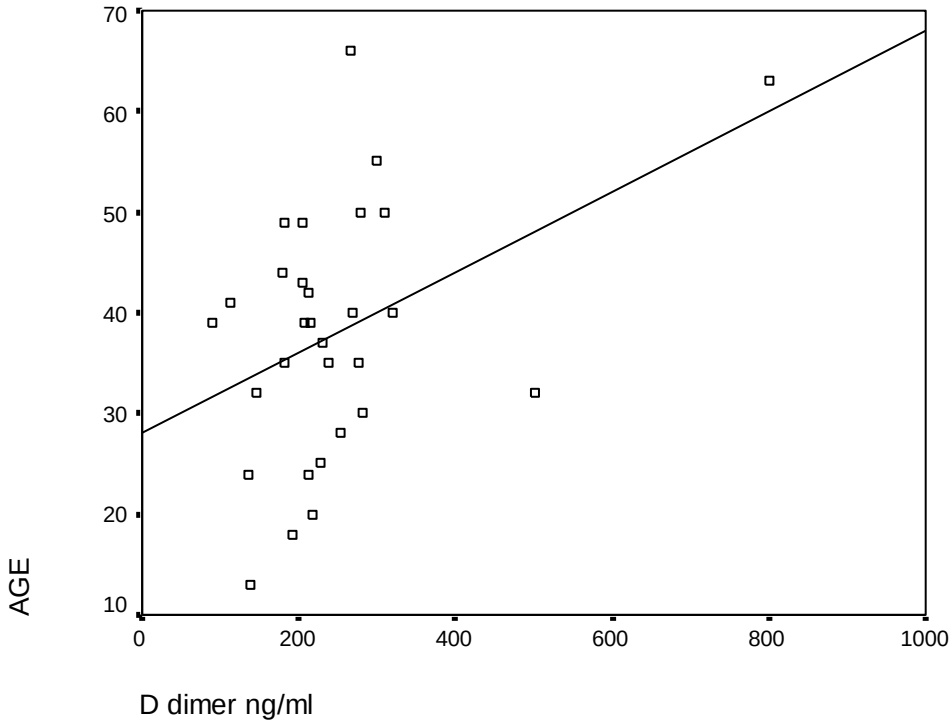


Figure (3.2): correlation between D-dimer and age group

Week positive correlation (p.*value*= 0.02, r= 0.41)

3.6 Correlation between D-dimer and TSH in thyroid abnormalities patients

Standing correlation between D-dimer and TSH showed that there was no correlation between them Figure (3.3).

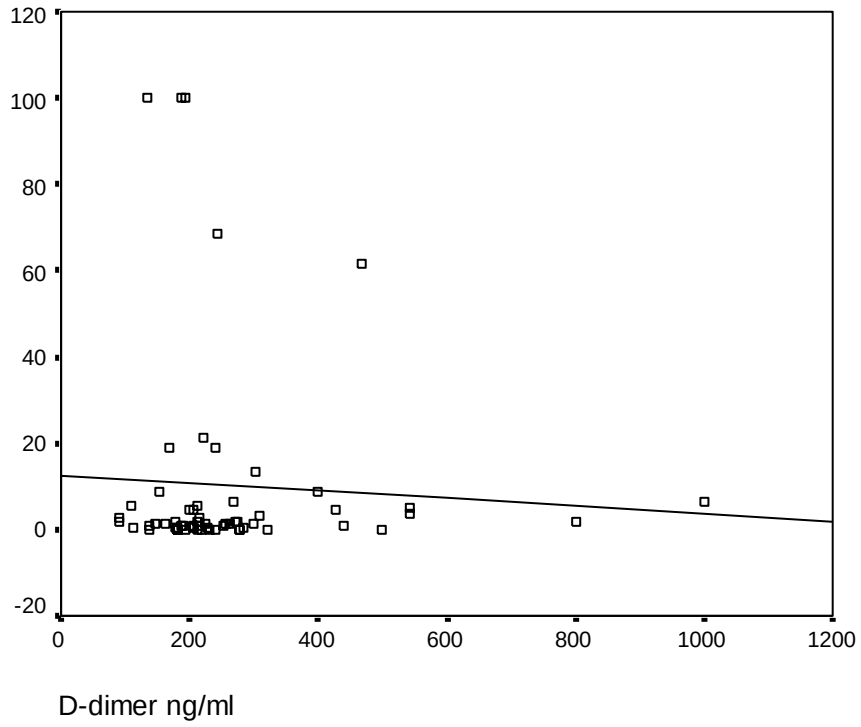


Figure (3.3): correlation between TSH and D-dimer (p.*value*= 0.6, r= -0.05)

3.7 Correlation between D-dimer and T3 in thyroid abnormalities patients

Standing correlation between D-dimer and T3 showed that there was no correlation between them figure (3.2).

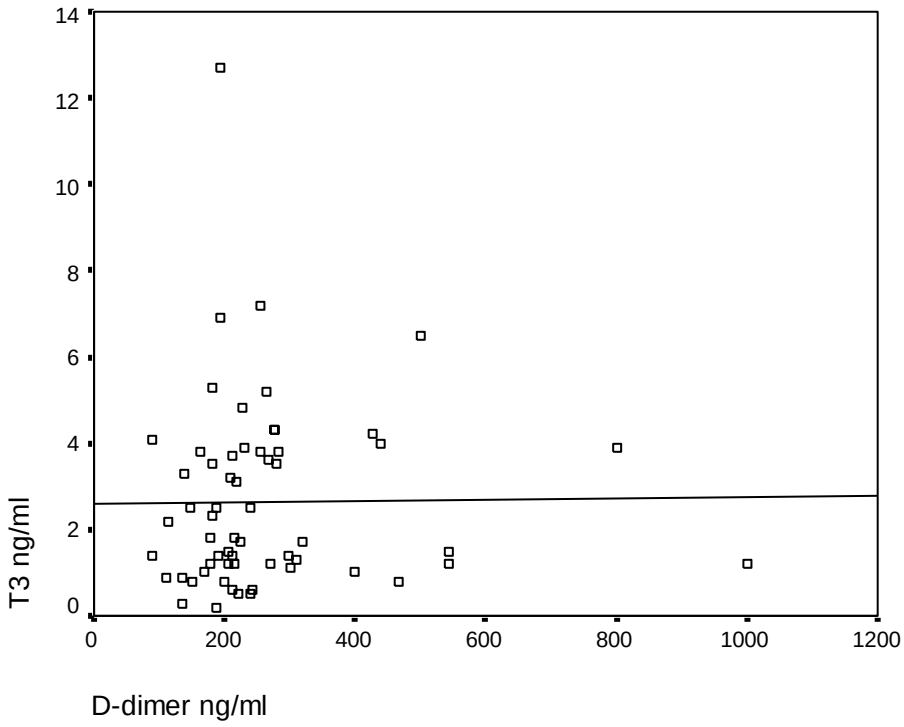


Figure (3.4): correlation between T3 and D-dimer (*p.value*= 0.9, r= 0.01)

3.8 Correlation between D-dimer and T4 in thyroid abnormalities patients

Standing correlation between D-dimer and T4 showed that there was no correlation between them figure (3.3).

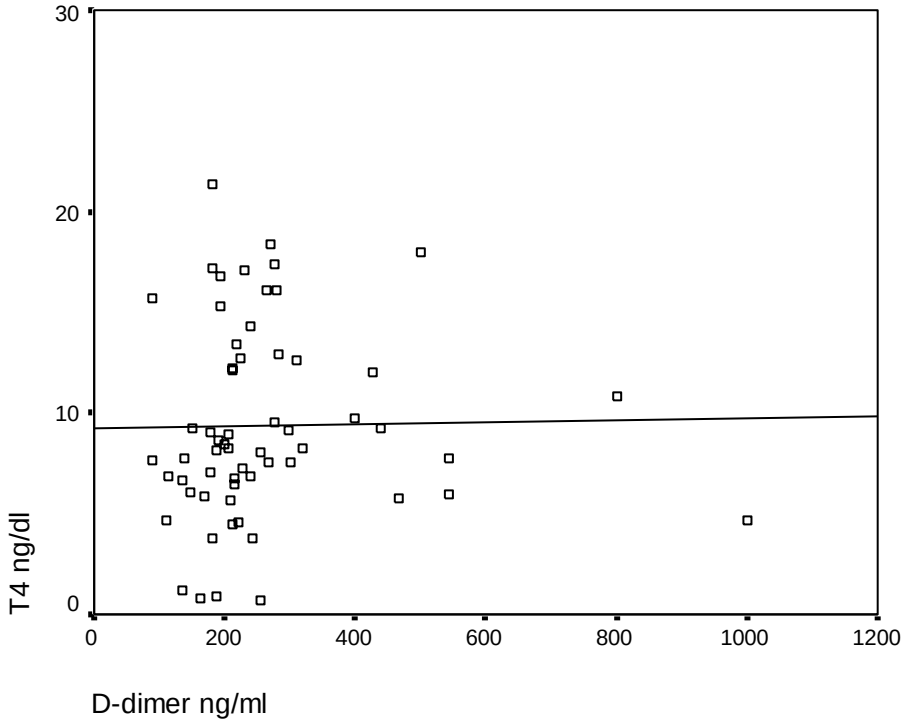


Figure (3.5): correlation between T4 and D-dimer (*p.value*= 0.8, r= 0.02**)**

3.9 Comparisons between D-dimer and study group

Using one sample T Test there is no significant difference in D-dimer between hypothyroidism and hyperthyroidism patients ($p : > 0.05$), The mean of D-dimer in hypothyroidism and hyperthyroidism (280ng/ml) (246ng/ml) respectively (table 3.3).

Table (3.3): Comparisons between D-dimer and thyroid abnormalities patients.

D-dimer ng/ml	N	Mean	Std. Deviation	P. *Value*
hypothyroidism	30	280.09	182.08	0.4
hyperthyroidism	30	246.11	130.00	

Chapter Four

Discussion, Conclusion and Recommendations

Chapter four

4.1 Discussions

This study include 60 female diagnosed as thyroid dysfunction classified as 30 hypothyroidism and 30 hyperthyroidism patients, to measure the D-dimer level.

The study showed that normal level of D-dimer in hypothyroidism patients under treatment and this result agree with report of (Lupoli *et al*., 2015) were conclude that sub clinical hypothyroidism patients exhibit a prothrombotic status, which is reverted by a 6-month L-T4 treatment.

A weak but significant positive correlation was observed between the d-dimer and age of hypothyroidism (r= + 0.42, p. *value* = 0.019).

The present study showed that normal level of D-dimer in hyperthyroidism patients under treatment (radio iodine and Carbimazole) and this agree with report of (Mazur *et al.*, 2014) whom found that after 3months of thyroid function normalizing therapy (91.4%) hyperthyroid and (85.7%) hypothyroid subjects achieved euthyroidism and had improved fibrin clot properties with normalization. There was no correlation between T4 and D-dimer level in hyperthyroidism patients this result disagree with report of (Brona *et al*., 2011) whom found TSH, fT4 and fT3 correlated with D-dimer level in overt hyperthyroidism.

According to correlation between d-dimer and age of hyperthyroidism patients the result showed that a weak significant positive correlation (r= + 0.41, p. *value* = 0.02).

The result showed that no significant differences in D-dimer level and BMI ,duration time of disease (p.*value* 0.7 and 0.9)respectively , no published data

found agree with this study because all standing done in this field were longitudinal studies which allow informative data.

4.2 Conclusion

1- All patients with hypothyroidism and hyperthyroidism on treatment presented normal D-dimer level.

2- Positive correlation between D-dimer and age group in thyroid abnormalities patients.

3-No significant different in D-dimer level in hypothyroidism and hyperthyroidism patients.

4.3 Recommendation

1-we recommended to Measure other thrombotic marker rather than D-dimer like PAI-1 to show if there different in result or not.

2- Further study performance to compare D-dimer in thyroid abnormalities patients using large sample size.

References

References

•**Abdel Monim, M.H**., Medani, A., Abdelsalam, A., Elnour, B and Amal, M .S. (2010). Iodine deficiency disorder in urban schoolchildren . *Bulletin of the World Health Organisation* **89**:121-126.

• **Adam, S.S**., Key, N.S., and Greenberg, C.S. (2009). D-dimer antigen: current Concepts and future prospects . *Blood,* **113** (13): 2878–2887.

• **Akamizu, T**., Satoh ,T., and Isozaki, O.(2012).Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. *Thyroid.*

•**Akinci , B .,** Comlekci ,A., and Ozcan, M.A,(2011). The alteration of coagulation in patients with thyroid dysfunction. *Recent Patent on Endocrine and Metabolic Immune Drug Discovery*, **5**(1):50–7.

• **Andersson** ., Maria., Zimmermann. , and Michael B. (2010). "Influence of Iodine Deficiency and Excess on Thyroid Function Tests". *Endocrine Updates*. **28**: 45–69.

• **Baglin** , Trevor., Keeling., David., Kitchen. and Steve. (2012). "Effects on routine coagulation screens and assessment of anticoagulant intensity in patients taking oral dabigatran or rivaroxaban: Guidance from the British Committee for Standards in Haematology*". British Journal of Haematology*. **159** (4): 427–429.

• **Baklaja, R**., Pešic,´ M.C., and Czarnecki, J. (2008). Hemostatic and Hemorrhagic disorders, 3rd edition. Germany; Fermentation-Biotecc GMbH.Rodolf-Huch-str.14.

• **Bauer, D.C**. (2013). Pathophysiology of Disease: An Introduction to Clinical Medicine, 7th Edition. New York, NY .

• **Barbesin , G.,** and Tomer, Y.(2013). Clinical Utility of TSH Receptor Antibodies *The Journal 0f Clinicical Endocrinoly and Metabolisim*, **98**(6):2247-55.

• **Bishop, M**. and Edward, P. (2010).Clinical chemistry principle procedure correlation, 6th ed.

• **Brona, A** ., Bohdanowicz-Pawlak, A., Jędrzejuk, D., and Milewicz A.(2011) fibrinogen and D-dimer level in patients with hyperthyroidism before and after radioiodine therapy , *endokrynologia_polska* , **62** (5):409-15.

• **Brotfain, L**., Koyfman, A., Frenkel, A., Smolikov, A. Zlotnik, And M. Klein. (2013). Iodine-induced hyperthyroidism—an old clinical entity that is still relevant to daily ICU practice: a case report, *National Institutes of Health's National Library of Medicine* , 2013(1):792745, 4 pages.

• **Chakera**, A.J., Pearce, S.H., and Vaidya, B. (2012). "Treatment for primary hypothyroidism: current approaches and future possibilities" Drug Design, *Development and Therapy* , **6**: 1–11.

• **Chang**, R.Y., Lang, B. H., Chan, A. C. (2014) Evaluating the efficacy of primary treatment for graves' disease complicated by thyrotoxic periodic paralysis. *International Journal of Endocrinology* , **1**(3): 182–186.

• **Charlton**, K., and Skeaff, S. (2011). Iodine fortification. *Current Opinion in Clinical Nutrition and Metabolic Care*, **14** (6): 618–624.

• **Ciesla, B**. (2007). Hematology in Practice, F.A.Davis company 2nd eddition. Philadelphia, USA.

• **Danka, J. F**., Stuijver, Bregje van Zaane , Erica Romualdi , Dees, P. M. Brandjes, Victor, E. A, Gerdes , and Alessandro Squizzato(2012). *Thrombosis and Haemostasis*, **108**:1077-88.

• **Danescu, L.G** ., Badshah , A ., Danescu , S.C ., Janjua , M ., Marandici, A. M ., Matta , F ., Yaekoub, A.Y ., Malloy, D.J., and Stein, P.D.(2009). Venous thromboembolism in patients hospitalized with thyroid dysfunction. International Academy of *Clinical* and *Applie Thrombosis /Hemostasis* **, 15**:676–680

- **David**,G.G., and Dolores, M. S. (2011). Greenspan's basic & clinical endocrinology (9th ed.). New York: McGraw-Hill Medical, 50-77.
- **DeLloyd, A.,** Bursell. J, Gregory, J.W., Rees. D.A. and Ludgate, M. (2010).TSHreceptor activation and body composition. *Journal of Endocrinology* , 204: 13–20.
- **Elaine**, **N. M**., and Hoehn, K. (2010). Human Anatomy & Physiology (8th ed.). San Francisco: *Benjamin Cummings*, 649–50.
- **Franklyn, J.A.,** and Boelaert, K., (2012).Thyrotoxicosis. *Lancet*, **379**(9821):1155-66.
- **Furie, B**. (2009).Pathogenesis of thrombosis. Hematology Am Soc Hematol Educ Pallister CJ, Watson MS (2010). Haematology. Scion Publishing., 336–347.
- **Gaitonde, D. Y**., Rowley, K. D., and Sweeney, L. B. (2012).Hypothyroidism: An update. *American Family Physician,* **86**(3): 244-251.
- **Garber, J.R**., Cobin, R.H., Gharib, H., Hennessey, J.V. Klein, I. Mechanick , J.I. Pessah, Pollack, R. and Singer, P.A. (2012). "Clinical Practice Guidelines for Hypothyroidism in Adults" (PDF). *Thyroid*, **22** (12): 1200–1235.
- **Glick, A. B**., Wodzinski, A. F. U. P., Levine, A . D., and Wald, D. N. (2013). Impairment of regulatory t-cell functions in autoimmune thyroid disease. *American Thyroid Association*. **23**(**7**): 871-878.
- **Goodman, C**., and Fuller, K. (2009) Pathology: Implications for the Physical Therapist, 3rd edition Saint Louis, Missouri: Saunders Elsevier, 301-13.
- **Hall** J.E. (2010). Guyton and Hall Textbook of Medical Physiology: Enhanced E-Book. 11th ed. Philadelphia: Elsevier Health Sciences; Hemostasis and blood coagulation, 457–9.
- **Hampton, J.** (2013). Thyroid gland disorder emergencies: Thyroid storm and myxedema coma. *AACN Advanced Critical Care*, **24**(3), 325-332.

- **Hoffbrand, A.V.,** Moss, P.A. H., and Pettit, J.E. (2006). Essential Hematology, 5th edition, black well publishing, Ltd, USA.
- **Holm, G.** (2012). Primary hypothyroidism, **16**(2):204-213.
- **Hooper**, J.M.W., Stuijver, D.J.F., Orme , S.M., van Zaane, B. ,Hess, K. Gerdes, V.E., Phoenix, F., Rice, P., Smith, K.A., and Alzahrani S.H.(2012). *The Journal of Clinical Endocrinology & Metabolism*, **97**:1463–1473.
- **Jabbar, A.,** and Razvi, S.(2014) .Thyroid disease and vascular risk, **14** (6):29-23.
- **Kabrhel, C.,** Mark Courtney, D., Camargo, C.A., Plewa, M.C. Nordenholz, K.E. Moore, C.L. Richman, P.B. Smithline, H.A. Beam, D.M. and Kline, J.A.(2010)."Factors Associated With Positive D-dimer Results in Patients Evaluated for Pulmonary Embolism" . *Academic Emergency Medicine*, **17** (6): 589–597.
- **Karlsson, O.** (2014). Hemostasis during pregnancy, labour and post partum Hemorrhage, *international journal of of obestractic anathesia*,**23**(1):10-7.
- **Klubo** , Gwiezdzinska, J., and Wartofsky, L . (2012). Thyroid emergencies, *Medical Clinics of North America.* , **96**(2):385-403.
- **Lupoli, R.,** Di Minno, M.N., Tortora, A., Scaravilli, A., Cacciapuoti, M., Barba, L., Di Minno, A., Ambrosino ,P., Lupoli ,G.A., and Lupoli, G.(2015). Primary and Secondary Hemostasis in Patients With Subclinical Hypothyroidism: Effect of Levothyroxine Treatment , *Journal of clinical endocrinology and metabolism*. **100** (**7**): 2659-2665.
- **Longo, D.L** ., Fauci , A. S., Kasper, D. L., Hauser, S. L., Jameson, J. L. and Loscalzo, J . (2011). "341: disorders of the thyroid gland". Harrison's principles of internal medicine. (18th edition) .

• **Long** , Andrew, T., Kenne, Ellinor, Jung ,Roman , Fuchs, Tobias, A., Renné, And Thomas. (2015). "Contact system revisited: An interface between inflammation, coagulation, and innate immunity". *Journal of Thrombosis and Haemostasis*, **14**:427–437.

• **Malcolm, J.** (2013). in A Comprehensive Guide to Toxicology in Preclinical Drug Development,(1st edition).

• **Machlus, K.R.**, and Italiano, J.E .(2013). The incredible journey: From megakaryocyte development to platelet formation. *Journal of Cell Biology* ,**201(**6):785-796.

• **Mackman, N**., and Triggers (2008),.targets and treatments for thrombosis. *Nature*, **451**:914–918.

• **Marieb,** Elaine ., Nicpon ., Hoehn, and Katja. (2010). Human Anatomy & Physiology (8th ed.). San Francisco: *Benjamin Cummings*, 649–50.

• **Marongiu, F.**, Cauli, C., and Mariotti, S. (2004) Thyroid, hemostasis and thrombosis. *Journal of Endocrinology* ,**27**:1065–1071.

• **Mason, K.D**., Carpinelli, M.R., Fletcher, J.I., and Collinge, J.E. (2007) . Programmed anuclear cell death delimits platelet life span. Cell. **128**(6):1173–1186

•**Mazur, P** ., Sokołowski, G ., Hubalewska-Dydejczyk, A., Płaczkiewicz-Jankowska, E . Undas, A. (2014). Prothrombotic alterations in plasma fibrin clot properties in thyroid disorders and their post-treatment modifications. *Thrombosis Research*. **134**(2):510-7

• **Mirza, F.,** and Canalis, E. (2015). Management of endocrine disease: Secondary osteoporosis: pathophysiology and management, *european journal of endocrinology* .**173**(3):R131-51.

•**Nakashima, Y.,** Kenzaka, T., and Okayama M. (2014).A case of thyroid storm with cardiac arrest. *International Medical Case Report Journal*, **87**:89-92.

• **Nicki, R. C**., Brian , R. W., and Stuart, H. R. (2010). Davidson's principles and practice of medicine. (21st eddition.). Edinburgh: Churchill Livingstone/Elsevier

•**Pallister, C.J**., and Watson, M.S.(2010). Haematology. 2nd editin . United Kingdom, london : Scion Publishing Ltd . 336–347.

• **Pober, J. S**., and Sessa,W.C.(2007), Evolving functions of endothelial cells in inflammation. *Nature Reviews Immunology* ,**7**:803–815.

•**Randolph, G.W.**, Shin ,J.J., and Grillo HC(2011).The surgical management of goiter: Part II. Surgical treatment and results. *Laryngoscope*,**121**(1):68–76.

•**Smith,** Terry, J., Hegedüs, and Laszlo. (2016). "Graves' Disease *". New England Journal of Medicine*. **375** (16): 1552–1565.

• **Squizzato, A.,** Gerdes, V.E.A ., Brandjes, D.P.M ., Buller, H.R and Stam, J. (2005) Thyroid diseases and cerebrovascular disease. *Stroke* , 36:2302–2310.

• **Stuijver, D.J.,** van Zaane . B, Romualdi ,E . Brandjes , D.P., Gerdes ,V.E., and Squizzato, A(2012). The effect of hyperthyroidism on procoagulant, anticoagulant and fibrinolytic factors. A systematic review and meta-analysis. Thrombosis and Haemostasis, *European Journal of Endocrinology* **108** :1077–1088.

•**Suzuki, T.,** Distante, A., and Eagle, K. (2010). "Biomarker-assisted diagnosis of acute aortic dissection: How far we have come and what to expect". *Current Opinion in Cardiology*. 25 (6): 541–545.

•**Tsai, M.S.,** Chuang, P.Y., Huang, C.H.(2015). Better adherence to antithyroid drug is associated with decreased risk of stroke in hyperthyroidism patients. *International Journal of Clinical Practical*,**96**(12):1473-1485.

•**Van Zaane, B.,** Squizzato, A., and Debeij, J.(2011). Alterations in coagulation and fibrinolysisafter levothyroxine exposure in healthy volunteers: a controlled

randomized crossover study. *Journal of Thrombosis and Haemostasis*, **9**: 1816–1824.

• **Vanderpump**,**M.P**., (2011). "The epidemiology of thyroid disease," *British Medical Bulletin*, **99**:39–51.

•**Van Deventer, H.E.,** Mendu, D.R., Remaley, A.T., and Soldin ,S.J.,(2011). Inverse log-linear relationship between thyroid-stimulating hormone and free thyroxine measured by direct analog immunoassay and tandem mass spectrometry. *Clinical Chemistery*, **57**(1):122–127.

•**Varga, D.,** Pleines, I., and Nieswandt, B.(2008). Cell adhesion mechanisms in platelets. *Arterioscler Thrombosis and Vascular Biology*, **28**:403–412

• **Yango,** J., Alexopoulou , O., Eeckhoudt , S., Hermans, C., and Daumerie , C.(2011) , Departments of Endocrinology and Hematology. *European Journal of Endocrinology* , **164** :599–603.

•**Zaletel , K.,** and Gaberščck, S., (2011). Hashimoto's Thyroiditis: From Genes to the Disease , *Current Genomics*. **12**(8): 576–588.

• **Zimmermann, M.P.**, Jooste , C. S., and Pandav, C.S., (2008). Iodine-deficiency disorders, *lancet (London-England)*,**372**:1251–1262.

• **Zimmermann M.P.,** (2013). "Iodine deficiency and excess in children, *Endocrine Practice*, **19**:839–846.

• **Xiao, T.,** Takagi, J., Coller, B. S., Wang, J.H., and Springer, T.A. (2004). Structural basis for allostery in integrins and binding to fibrinogen-mimetic therapeutics. *Nature*, **432**:59–67

Appendixes

Appendix I

بسم الله الرحمن الرحيم

Sudan University of Science and Technology

Collage of graduate studies –department of hematology

Questionnaire: D-dimer in thyroid dysfunction patients

Name:

Age:

Residence:

Body mass index:

Type of thyroid abnormalities:

Duration time of disease:

treatment use:

Family history:

Telephone:

Result: **TSH:** **mIu/I** **T3:** **ng/ml**

T4: **ng/dl** **D-dimer:** **ng/ml**

Appendix II

اقرار الموافقة

انا الباحث أيمان عبدالغني بصدد قياس معدل الدي دايمرعند النساء المصابات بخلل في الغدة الدرقية بعد فترة العلاج ونقوم بجمع المعلومات وعينات دم وريدي منك لعمل الفحوصات اللازمة في حالة الموافقة علي المشاركة وفي حالة حدوث اي مضاعفات ارجو الرجوع الي.

بعد الفهم التام لمحتوي الاستبيان اوافق علي جمع العينات.

إسم المتبرع/ ..... العنوان/ .....

التوقيع...../

إسم الباحث...../ العنوان/ .....

التاريخ / /

Appendix III

Cobas e 411


I-CHROMA READER
www.sasmedica.com

.