بسم الله الرحمن الرحيم

Sudan University of Science And Technology

College of Graduate Studies

Evaluation of Prothrombin Time, INR and Activated Partial Thromboplastin Time among Pulmonary Tuberculosis Patients in Khartoum State

تقييم زمن البروثرومبين, **INR** و زمن الثرومبوبلاستين الجزئي المنشط عند مرضى السل الرئوي في ولاية الخرطوم

Dissertation submitted in a partial fulfillment of the requirements for the award of the degree of M.Sc. in Hematology and Immunohematology

Submitted by:

Shaimaa Mustafa Ismail Elhag

(B.Sc. in H. Hematology and Immunohematology, SUST, 2014)

Supervisor:

Dr. Kawthar Abdalgaleil Mohammed Salih Ibrahim

(Ph.D in Immunology, U of K, 2014)

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الآيـة

بسم الله الرحمن الرحيم

قال تعالى:

وَلِلّــهِ مُلْكُ السّمَاوَاتِ وَالْأَرْضِ يَغْفِرُ لِمَن يَشَاءُ وَيُعَذِّبُ مَن يَشَاءُ وَكَانَ اللّــهُ غَفُورًا رّحِيمًا ﴿١٤﴾

صدق الله العظيم

سورة الفتح الآية 14

Dedication

To…my lovely mother

To…my father soul

To…my dears brothers

To …my darling teacher MudathirAbdelrahim

To…my special friends ,teachersand colleagues who support me…… I dedicate this work…

Shaimaa….

Acknowledgment

Great thanks firstly and finally to Allah who gave us the will to accomplish this work.

Firstly I would like to thank my wonderful teacher Dr. KawtharAbdalgaleilmohammedsalihfor her advice and encouragement to conduct this study.

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Grate thanks also for staff of hematology department and for everyone who help me to complete this study.

Finally thanks extended to all people whom the blood samples has been collected from.

Abstract

This was case control study, conducted in Khartoum state at Aboanga hospital during the period from January to April 2017. The study aimed to evaluate some coagulation parameter (PT,INR andAPTT) in pulmonary tuberculosis patients.

Study include 50 active TB patients (cases) and 50 non TB patients (control), all subject were informed verbally about the study and approved for participation. from each participant 1.8ml of venous blood collected in tri sodium citrate anticoagulant container in a ratio of (1:9), centrifuged to prepare platelet poor plasma from which targeted parameter (PT,INR andAPTT) measured using coagulation analyzer (diagondia timer-2).

Results analyzed by independent T-test and Pearson correlation test by SPSS (version 11.5) computerized program.

Demographic data collected through questionnaire showed that most of study participant were males78 % (39/50) rather than females 22%(11/50) ,44%(22/50) were smoker while 56%(28/50) are non-smoker, and Age of participated TB patients distributed from 16-58 years with mean age of 32+/- 11years.

Age divided in to three age groups(15-30), (31-45)and (46-60) years. age group of (15-30) years was most frequent48% (24/50), while group of (46-60) years have the least frequency among cases 12% (6/50).

The result obtained from patients show that means of PT,APTT and INR are (16second, 46 second and 1.2) respectively, and it was reflect that there is clear significant difference in APTT (*p. value* 0.000) between

cases and control group while there is slight significant difference in PT(*p. value* 0.053) and INR (*p. value* 0.052) between them.

Results also show that there is no significant difference in measured parameter (PT, INR andAPTT) between smoker and non-smoker(*p. values* 0.51, 0.55, 0.63) respectively. And same results obtained for sex groups (p. values 0.23, 0.21, 0.56) respectively.

Finally the result show presence of weak positive correlation between (PT/APTT) and (INR/APTT) P and r values are 0.035/ 0.300 and 0.041/ 0.291 respectively.

مستخلص البحث

اجريت هذه الدراسة بطريقة حاله مقارنة بحاله ضابطه في ولاية الخرطوم في مستشفى ابو عنجه خلال الفترة الزمنية من يناير إلى ابريل 2017.

هدفت هذه الدراسة الى تقييم بعض معاملات تخثر الدم (زمن البروثرومبين , زمن الثرومبوبلاستين الجزئي المنشط و INR) في مرضى السل الرئوي.

تضمنت هذه الدراسة 50 مريض سل رئوي (حاله) و50 شخص غير مصابين بالسل الرئوي (حاله ضابطه).

اخطر كل المشاركين في الدراسة شفاهه عن مفهومها واخذت موافقتهم على المشاركة.

تم جمع 1.8 ملي لتر من الدم الوريدي في حاوية مانع التجلط ثلاثي سترات الصوديوم بمعدل(1:9) من كل مشارك, ثم تم تحضير المصل الدموي قليل الصفائح الدموية ومنه تم قياس معاملات التخثر المستهدفة (زمن البروثرومبين , زمن الثرومبوبلاستين الجزئي المنشط و INR) باستخدام محلل التخثر (دايقون دياتايمر-2).

حللت النتائج ب بواسطه برنامج الحزم الاحصائيه للعلوم الاجتماعيه اصدار11.5.

جمعت البيانات الديموغرافية (السكانية) عن طريق استبيان واوضحت ان معظم اعضاء الدراسة من الذكور 78% (50/39) فضلا عن الاناث 22% (50/11) وان 44%(50/22) مدخنين بينما 56%(50/28) غير مدخنين,وان اعمار مرضى السل الرئوي المشاركين تراوحت ما بين ال16-58 سنه بمتوسط عمري 32+/-11سنه.

تم تقسيم المرضي المشتركين في الدراسة على حسب الاعمار الى ثلاث فئات (15-30), (31-45) و(46-60) سنه.الفئه من (15-30) سنه هي الاكثر ترددا 48%(50/24) بينما فئه (46-60) هي الاقل ترددا بين المرضى 12%(50/6).

دلت النتائج المتحصل عليها على ان متوسطات زمن البروثرومبين , زمن الثرومبوبلاستين الجزئي المنشط و INR هي (16 ثانيه, 46 ثانيه و 1.2)علي التوالي.

اشارت النتائج الى وجود فرق واضح ذو دلاله إحصائية في زمن الثرومبوبلاستين الجزئي المنشط (القيمة المعنوية 0.000) في الحالة مقارنة بالحالة الضابطة بينما اشارت ايضا الى وجود

فرق طفيف ذو دلاله إحصائية في زمن البروثرومبينINR (القيم المعنوية0.053 و0.052) على التوالي في الحالة مقارنة بالحالة الضابطة.

كما اظهر التحليل ايضا عدم وجود فرق ذو دلاله إحصائية في معاملات التخثر المقاسة (زمن البروثرومبين , زمن الثرومبوبلاستين الجزئي المنشط و INR) بين المدخنين وغير المدخنين (القيم المعنوية0.518, 0.633 و0.556)على التوالي و ذات النتيجة المذكورة اعلاه تم الحصول عليها بالنسبة لفئتي الجنس (القيم المعنويه0.231, 0.568 و0.215) على التوالي.

ختاما اشارت النتائج الى وجود ارتباط ايجابي ضعيف بين زمن البروثرومبين / زمن الثرومبوبلاستين الجزئي المنشط (القيمة المعنوية 0.035) وقيمة الارتباط (0.30) و وجود ارتباط ايجابي ضعيف ايضا بين INR / زمن الثرومبوبلاستين الجزئي المنشط (القيمة المعنوية 0.041) وقيمة الارتباط (0.29).

List Of Abbreviations:

Abbreviation	Full Name
ADP	Adensine Di Phosphate
AFB	Acid-Fast Bacilli
AHF	Anti-Hemophilic Factor
AHG	Anti-Hemophilic Globulin
AIDS	Acquired Immune Deficiency Syndrome
APTT	Activated Partial Thromboplastin Time
BCG	BacilleCalmetteGuérin
CMI	Cell Mediated Immunity
DIC	Disseminated Intravascular Coagulation
DNA	Deoxy Ribonucleic Acid
EDRF	Endothelium Derived Relaxing Factor
FSF	Fibrin Stabilizing Factor
HMWK	High Molecular Weight Kininogen
INH	Isoniazid
INR	International Normalize Ratio
ISI	International Sensitivity Index
NO	Nitrite Oxide
OD	Optical Density
PAS	Para-Aminosalicylic Acid
PC	Protein C
PF 3	Platelet Factor 3
Pg	Prostaglandin
PPP	Platelet Poor Plasma
PS	Protein S
PT	Prothrombin Time
PTA	Plasma Thromboplastin Antecedent

PTB	Pulmonary Tuberculosis
PTC	Plasma Thromboplastin Component
SD	Standard Deviation
SPCA	Serum Prothrombin Conversion Accelerator
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
TF	Tissue Factor
TFPI	Tissue Factor Pathway Inibitor
TM	Thrombomodulin
TNF	Tumor Necrosis Factor
t PA	Tissue Plasminogen Activator
TXA2	Thromboxane A 2
UV	Ultra Violet
VWF	Von Will Brand Factor

List Of Contents:-

List of tables:-

List of figures:-

Chapter One

Introduction & Literature Review

Introduction and literature review

1.1 Introduction:

Tuberculosis (TB) is a slow progressing chronic disease of human and animals caused mainly by *Micobacterium tuberculosis,* less commonly by *Micobacteriumbovis*and rarely by *Micobacteriummicroti*and *Micobacteriumafricanum*.Tuberculosis is one of most common diseases worldwide**,** with high morbidity and mortality rates,particularly in developing countries, immunocompromised and poorer communities (Irving *et al* ., 2005).

TB infection is usually acquired by the inhalation of droplet nuclei containing viable tubercle bacilli. Up to 7% of all deaths and 26% of preventable deaths in developing countries are due to TB. TB predominantly affects young adults in their most productive years of life and has substantial impact on economic development (Guerrant*etal*.,2004).

Coagulation is a complex network of interactionsinvolving vessels, platelets, and factors. The ability to form and to remove a clot is truly a system dependent on many synergistic forces. Hemostasis depends on a system of checks and balances between thrombosis and hemorrhage that includes both procoagulants and anticoagulants**,** this scale needs to be kept in balance (Ciesla, 2007).

The arresting of bleeding,depends on several components. The four major components are the vascular system, platelets (thrombocytes), blood coagulation factors, and fibrinolysis(Turgeon, 2005).

1.2 . literature review

1.2.1 Over view of hemostasis:

In the most simplistic terms, blood coagulation occurs whenthe enzyme thrombin is generated and proteolysis soluble plasma fibrinogen, forming the insoluble fibrin polymer, or clot, this provides the physical consolidation of vessel wound repair following injury (Hoffbrand*et al*., 2007).

The term come from the ancient greek roots "heme" meaning blood, and "stasis" meaning halting; but together meaning the halting of the blood (Marieb*et al*., 2010)

It refers more widely to the process whereby blood coagulation is initiated and terminated in a tightly regulated fashion, together with the removal (or fibrinolysis) of the clot as part of vascular remodeling; as such, hemostasis describes the global process by which vessel integrity and patency are maintained over the whole organism, for its lifetime (Hoffbrand*et al*., 2007).

1.2.2 Component of Normal hemostasis:

1.2.2.1 Blood vessel:

Blood vessel convey blood around the body and are classified in to three main types arteries, capillaries and vein (Glosing*et al*., 2008).

vessel wall is divided into three coats or tunics. These coats are the tunica intima, tunica media, and tunica adventitia. The tunica intima forms the smoothglistening surface of endothelium that lines the lumen (inner tubular cavity) of all blood and lymphatic vessels and the heart. It line with simple squamous epithelium referred to as endothelium. The tunica intima consists of a single layer of endothelial cells thickened by a sub endothelial connective tissue layer containing elastic fibers. The tunica media, the thickest coat, is composed of smooth muscle and elastic fibers.

The tunica adventitia consists of fibrous connective tissue that contains autonomic nerve endings and the vasa vasorum, small networks of blood vessels that supplynutrients to the tissues of the wall.The endothelium contains connective tissues such ascollagen and elastin which regulates the permeability of the inner vessel wall and provides the principal stimulus to thrombosis following injury to a blood vessel. It is also rich with plasminogen activator, which, in appropriate stimulation, is released and activates plasminogen, which ensures rapid lysis of fibrin clots.(Turgeon, 2005).

1.2.2.2 Platelets :

Platelets are made in the bone marrow. Huge cells known as megakaryocytes (derived from hematopoietic stem cells) are the precursor to platelets, one megakaryocyte can produce 2,000 platelets**.** Platelets bud off the edges of the megakaryocytewhich eventually perishes by evaporating. It circulates in the blood for 7-10 days. Its either circulate freely or sequestered in the spleen.at any given time one third of platelets are located in the spleen (Deloughery, 2004).

Platelets are extremely small and discoid, 3.0 x 0.5 micrometer in diameter, with a mean volume 7-11 fL.Thrombopoietin is the major regulator of platelet production and is constitutively produced by the liver and kidneys. (Hoffbrand*etal.*,2006).

1.2.2.3 Fibrinolytic system:

One process limiting the extent of clot formation is the fibrinolytic proteinSystem (Schmaier and Lazarus, 2012).

The principal effector of clot removal by which degradation of fibrin into smaller fragmentsoccurs through the action of plasmin. The components of the fibrinolytic pathway are plasminogen with endogenous and exogenous activators to form plasmin (Shinton, 2008).

plasmin is cleavedby tissue plasminogen activator (tPA) secreted by healthyvascular endothelial cells, or urokinase on the surface of macrophages, to the fibrinolytic enzyme plasmin. which cleaves fibrin into fibrin degradation products, notably theD-dimer fragment specific to cleavage of cross-linked fibrin (Porwit *et al.*, 2011).

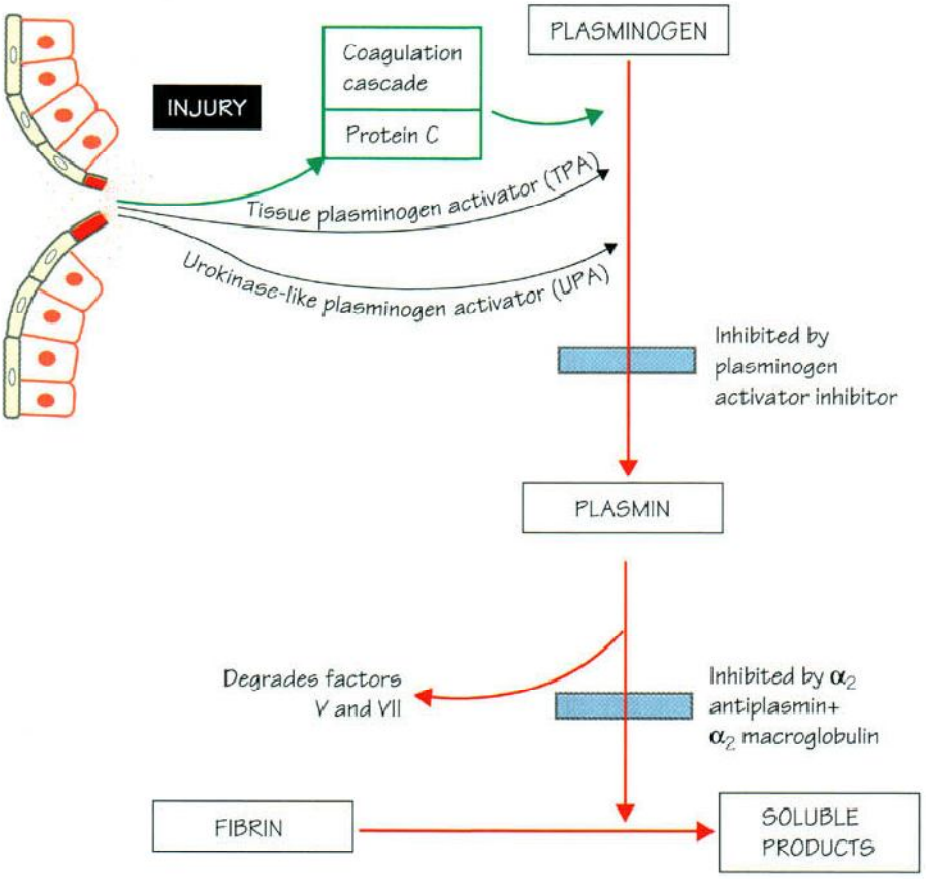

Figure A: Fibrinolytic system with the components of activation and inhibition (Mehta and Hoffbrand, 2000)**.**

1.2.2.4 Coagulation factors:

Bleeding from small blood vessels may be stopped by vasoconstriction and the formation of a platelet plug, but the formation of a clot (thrombus) usually occurs as part of the normal process of hemostasis. (Turgeon, 2005).

The soluble blood coagulation factors are critical components in the formation of a thrombus (table.A). Hepatic cells are the principal site of the synthesis of coagulation factors. However, other cells, such as endothelialcells, also play an important role in the normal process of hemostasis and thrombosis. Classically, the coagulation factors have been described as reacting in a cascading sequence. Modifications of this sequence are now known to occur as the blood factors interact to form the final insolublegelatinous thrombus (Turgeon, 2005).

Table. A:Protein of blood coagulation:(Turgeon, 2005).

Factor	**Name**	**Alternate Terms**
I	Fibrinogen	
II	Prothrombin	
V	Proaccelerin	Labile factor, Ac globulin
VII	Proconvertin	Stabile factor, SPCA
VIII	AHF	AHG, anti-hemophilic factor A
IX	PTC	Christmas factor, anti-hemophilic factor B
X	Stuart factor	Stuart-Prower factor
XI	Plasma thromboplastin antecedent	PTA, anti-hemophilic factor C
XII	Hageman factor	Glass or contact factor
XIII	Fibrin-stabilizing factor	FSF
Others	*Prekallikrein*	*Fletcher factor*
	HMW kininogen	HMW kininogen, Fitzgerald factor
	vWF	Factor VIII–related antigen
	Fibronectin	

	Anti-thrombin III	
	Heparin cofactor II	
	Protein C	
	Protein S	

1.2.2.5 Coagulation inhibitor:

There are three separate mechanisms to this aspect,and they all are to do with control of the productionand function of thrombin which are Circulating antithrombin, The protein C/thrombomodulin mechanism and Tissue factor pathway inhibitor activation.Anti-thrombincomplexes with thrombin, thereby inactivating it, but in addition has other anti-coagulant actions by inactivating XIIa, XIa, IXa, and Xa. Thrombomodulin on the surface of intact endothelial surfaces, binds both thrombin and protein C (and the binding to protein C is stronglyenhanced by the protein C receptor on the endothelium). Within this bound complex, thrombin loses its procoagulant properties and becomes an anti-coagulant, by the process of activating protein C. Activatedprotein C, on the surface of activated platelets (wherethe coagulation process is going on), degrades Va and VIIIa, thus inhibiting further local coagulation. proteins C and S also require vitamin K-dependent post-translational carboxylation for effect this is important when considering coagulation disorders in liver disease and in instituting anti-coagulant therapy (Beck., 2009).

Tissue factor path way inhibitor (TFPI)bind to factor Xa and in this combination, binds to and inhibits tissue factor/factor VII complex and activated factor X (Xa), TFPI synthesize primarily by endothelium, other part found as blood porn and tiny portion is found in platelet (AbdelGader, 2009).

1.2.3 Role of Vitamin K in hemostasis:

Factors II, VII, IX, X, protein C and protein S have vitamin K dependent Glutamic Acid domains in amino terminusof the protein. These domains contains 9-11 Glutamic acids modified to form gamma-carboxyglutamic acid. This modification allows calcium to bind to proteins. The binding of calcium changes the conformations of the proteins and serves to bind them in turn to phospholipid surfaces. The hepatic Glutamic acid redox reaction is dependent on vitamin K. without this vitamin, dysfunctional coagulation proteins are produced which function poorly in coagulation reactions (Deloughery, 2004).

1.2.4 Mechanism of Normal Hemostasis:

Hemostasis occur when blood is present outside of the body or blood vessel. 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 vessel to constrict to allow less blood to be lost in the second step, platelet plug formation, platelet 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" (www. Hemostasis.com).

1.2.5 Primary hemostasis:

This is normally triggered by an injury to the endothelium. This produces a gap in the tissues that is immediately filled with blood from the damaged vessel(s). The blade cuts through the tissues, through the sub endothelium, and then through the endothelium, producing a gap. The blade is withdrawn, and blood immediately fills the gap (Beck., 2009).

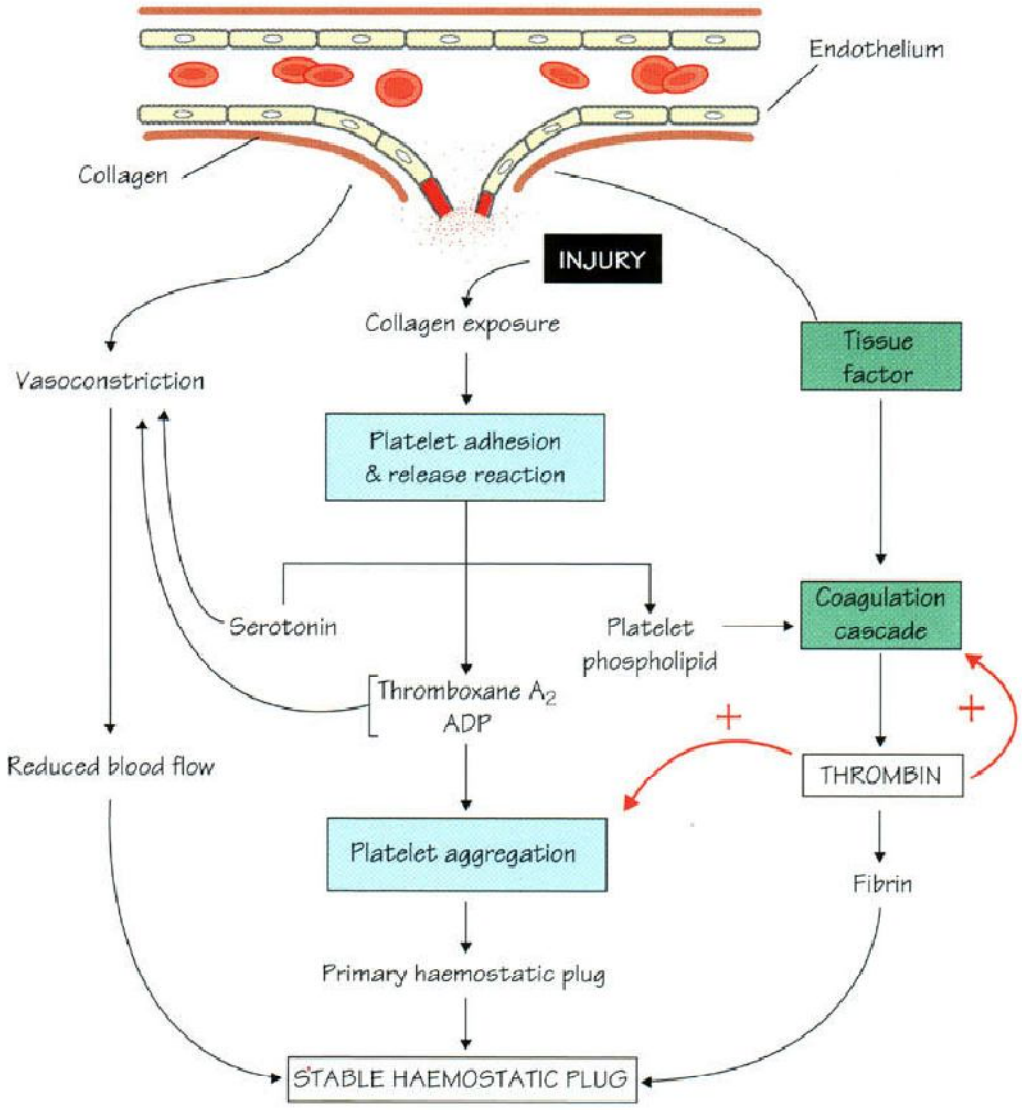

Figure B: Normal hemostasis(Mehta and Hoffbrand., 2000).

1.2.5.1 Vascular and Endothelial function in hemostasis:

Normal, intact endothelium does not initiate or support platelet adhesion andblood coagulation. Endothelial thromboresistance is caused by a number of antiplatelet and anticoagulant substances produced by the endothelial cells. Important vasodilators and inhibitors of platelet function are prostacyclin (prostaglandin I2, PgI2) and nitrite oxide (NO), formerly called endothelium-derived relaxing factor (EDRF). Small blood

vessels comprise arterioles, capillaries, and venules. Only arterioles have muscular walls, which allow changes of the arteriolar caliber. Upon contraction, arterioles contribute to hemostasis, thus temporarily preventing extravasation of blood. Platelet secretion of thromboxane A2, serotonin, and epinephrine promotes vasoconstriction during hemostasis (Munker*et al.*, 2007**).**

Vascular spasm is the blood vessel first response to injury, vasoconstriction occur which reduce the amount of blood flow through the area, this triggered by factors such as a direct injury to vascular smooth muscle, chemical released by endothelial cells and platelets, vascular spasm is much more effective in smaller blood vessel (www. Hemostasis.com).

Damaged endothelial release VWB factor which it is main function to mediate adhesive interactions of platelets exposed to rapid blood flow, there are two distinct platelets receptors for VWB factor the glycoprotein (GP) Ib and GP IIb-IIIa (Rugggeri, 2003).

1.2.5.2 Role of platelets in hemostasis:

In a healthy blood vessel, and under normal blood flow, platelets do not adhere to surfaces or aggregate with each other. However, in the event of injury platelets are exposed to sub endothelial matrix, and adhesion and activation of platelets begins (Jackson, 2007).

Platelets are a large factors in the hemostatic process. they allow the creation of the platelets plug that form almost directly after blood vessel has been ruptured (www. Hemostasis .com**).**

1.2.5.2.1 PlateletsAdhesion:

platelets adhereto the sub endothelial collagen fibers, spread pseudopods along the surface, and clump together (aggregate) when vascular injury exposes the endothelial surface and underlying collagen ,its adhesion to sub endothelial connective tissues, especially collagen, occurs within 1 to

2 minutes after a break in the endothelium. Epinephrine and serotonin promote vasoconstriction. ADP increases the adhesiveness of platelets. adhesion and aggregation of platelets are mediated by the binding of large soluble macromolecules to distinct glycoprotein receptors anchored in the platelet membrane, this increase the adhesiveness and cause circulating platelet to adhere to those already attached to the collagen resulting in cohesive platelets mass that rapidly increase in size to form platelet plug (Turgeon, 2001).

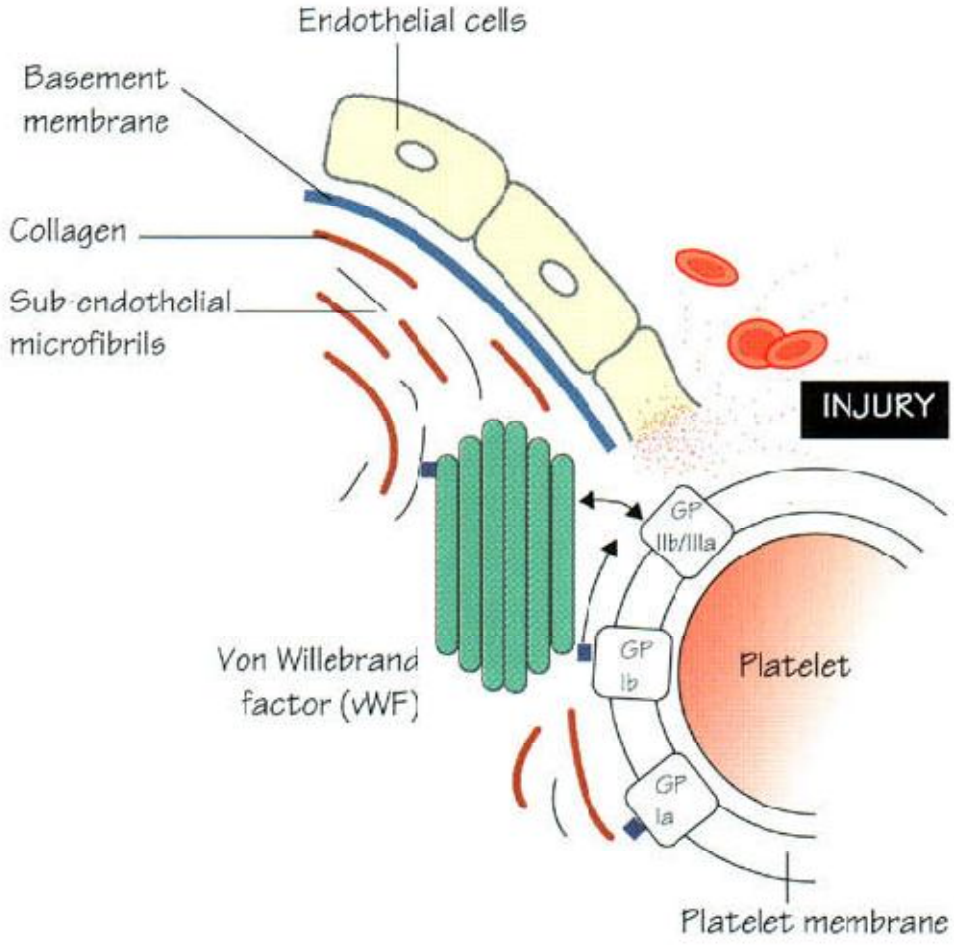

Figure C: Platelet adhesion (Mehta and Hoffbrand, 2000)

1.2.5.2.2Platelets aggregation:

It is the process in which adherent platelets becomeactivated and release the contents of storage granules, recruiting nearby platelets in circulation to form an aggregate , the formation of the platelet aggregate or thrombus occurs via activation of GPIIb-IIIa and binding of multivalent adhesive ligands, fibrinogen, or von Willebrand factor (vWF), which crosslink the adjacent activated platelets **(**White andJennings,1999).

1.2.5.2.3Platelets activation and release reaction:

Platelets undergo aggregation and release the content of their dense granule and *alpha* granule when exposed to agonist such as ADP, epinephrine, thrombin or collagen (Baklaja*et al*.,2008). ADP and serotoninreleased from the dense granules further enhance the platelet activation processes, for example, ADP released from the granules interacts with receptors on platelets to enhance the activation process (Schmaier and Lazarus, 2012).

1.2.6 Secondary hemostasis:

Secondary hemostasis consist of the cascade of coagulation serine proteases that cumulates in cleavage of soluble fibrinogen by thrombin, thrombin cleavage generates insoluble fibrin that form a crosslinked fibrin mesh at the site of an injury. fibrin generation occur simultaneously to platelets aggregation (Furie, 2009).

1.2.6.1Coagulation Pathways:

The plasmatic coagulation traditionally has been divided into two different pathways the intrinsic and extrinsic pathway. This understanding of coagulation has been built on studies of clotting in a relatively cell-free plasma system in vitro. However, such a division does not really occur in vivo because factor VIIa-TF complex is a potent activator of factor IX as well as factor X (Munker*et al*., 2007).

1.2.6.1.1 Extrinsic Coagulation Pathway:

The extrinsic pathway is initiated by the entry of tissue thromboplastin into the circulating blood. Tissue thromboplastin is derived from phospholipoproteins and organelle membranes from disrupted tissue cells. These membrane lipoproteins, termed tissue factors, are normally extrinsic to the circulation. Platelet phospholipids are not necessary for activation of the extrinsic pathway because tissue factor supplies its own phospholipids. Factor VII binds to these phospholipids in the tissue cell membranes and is activated to factor VIIa, a potent enzyme capable of activating factor X to Xa in the presence of ionized calcium. The activity of the tissue factor–factor VII complex seems to be largely dependent on the concentration of tissue thromboplastin. The proteolytic cleavage of factor VIIa by factor Xa results in inactivation of factor VIIa. Factor VII participates onlyin the extrinsic pathway. Membranes that enter the circulation also provide a surface for the attachment and activation of factors II and V. The final step is the conversion of fibrinogen to fibrin by thrombin (Turgeon., 2001).

1.2.6.1.2 Intrinsic Coagulation Pathway:

The intrinsic system assumes that exposure of contactfactors (factor XII, high-molecular-weight kininogens, prekallikrein) to an abnormalinjured vascular surface leads to activation of factor XI, which in turn activates factor IX, activated factor IX, in the presence of its cofactor factor VIII, then activates factor X to factor Xa in the presence of phospholipid. In turn, factor Xa with its cofactor factor V together form the prothrombinase complex, which converts prothrombin to thrombin, thrombin then converts fibrinogen to fibrin (Shinton, 2008).

1.2.6.1.3 Common Pathway:

Once factor X is activated to Xa, the extrinsic and intrinsic pathways enter a common pathway. Factor II, prothrombin, is activated to thrombin

(factor IIa), which normally circulates in the blood as an inactive factor (Turgeon., 2005).

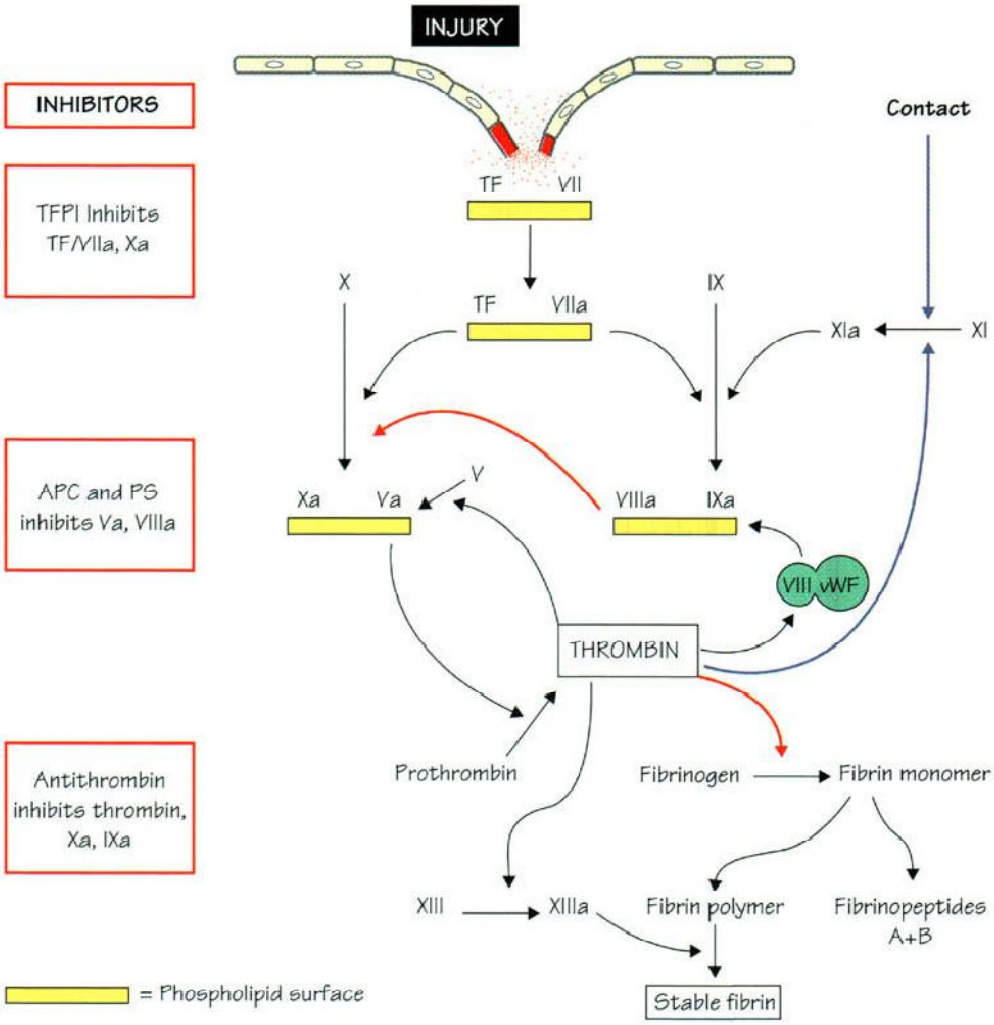

Figure D: The coagulation pathways: (Mehta and Hoffbrand, 2000)

1.2.7 Screening tests of blood coagulation

Screening tests provide an assessment of the 'extrinsic' and 'intrinsic' systems of blood coagulation and also the central conversion of fibrinogen to fibrin.The prothrombin time (PT) measures factors VII, X, V, prothrombin and fibrinogen. Tissue thromboplastin (a brain extract) and calcium are added to citrated plasma (Hoffbrand*etal*., 2006).

The International Sensitivity Index is a method of standardizing prothrombin times obtained from different laboratories. The INR is derived by dividing the patients prothrombin times by the control and raising this to the International Sensitivity Index (ISI). The ISI is known for each prothrombin laboratory reagent and it adjusts the prothrombin time for the differing sensitives of reagents. Using the INR instead of prothrombin time has resulted in more accurate monitoring of warfarin dosage. Many laboratories now only report the INR and not prothrombin time (Deloughery, 2004).

The activated partial thromboplastin time (APTT) measures factors VIII, IX, XI and XII in addition to factors X, V, prothrombin and fibrinogen. Three substances-phospholipid, a surface activator (e.g. kaolin) and calcium-are added to citrated plasma (Hoffbrand*et al*., 2006).

1.2.8 Tuberculosis:

Tuberculosis (TB) is an infectious disease of the lungs caused by the bacterium *Mycobacterium tuberculosis.* In the mid nineteenth century, about one-fourth of the mortality rate was attributable to tuberculosis. It was particularly rampant in early childhood and young adulthood. Its presence was felt throughout the world, but by the 1940s, with the introduction of antibiotics, there was a sharp decline of cases in developed countries. For less-developed countries with poor public health structures, tuberculosis is still a major problem. Since 1989, however, there has been an increase in reported cases in economically advanced countries due mainly to immunosuppression associated with AIDS, and the emergence of antibiotic-resistant strains of TB (Lerner *et al*., 2003).

it is a systemic infection manifested only by evidence of an immuneresponse in most exposed individuals. In some infected persons, the disease either progresses or, more commonly, reactivates after an asymptomatic period (years). The most common reactivation form is a

chronic pneumonia with fever, cough, bloody sputum, and weight loss. Spread outside of the lung also occurs and is particularly devastating when it reaches the central nervous system. The natural history follows a course of chronic wasting to death aptly called “consumption” in the past (Sherris*et al.*,2004).

The clinicaletiology of tuberculosis, a disease long known to man, was worked out in 1982 by R. Koch based on regular isolation of pathogens from lesions. Tuberculosis is unquestionably among the most intensively studied of all human diseases. In view of the fact that tuberculosis can infect practically any organ in the body, it is understandable why a number of other clinical disciplines profit from these studies in additionto microbiology and pathology (Kayser*et al.,* 2005).

The burden of TB is highest in Africa, Asia, India and China together accounting for almost 40 % of the world’s TB cases . About 2.4 million new TB cases and 540,000 TB-related deaths occur in sub-Saharan Africa annually **(** Kassa*et al*., 2016**).**

1.2.8.1 Epidemiology:

Tuberculosis occur in every part of the world, it is one of top 10 causes of death worldwide. In 2015 the largest number of new TB cases occurred in asia, with 61% of new cases followed by Africa, with 26% of new cases. Also in 2015 10.4 million people fell ill with TB and 1.8 million death from the disease (including 0.4 million among people with HIV) and over 95% of TB occur in low and middle income countries (WHO, 2017).

1.2.8.2 Causative agents:

The tuberculosis bacteria complex includes the species *M.tuberculosis*, *M. bovis*, and the rare species *M. africanum* (Kayser*et al.,* 2005).The genus *Mycobacterium* consists ofNonmotile, non–spore-forming, aerobic rods that are 0.2 to 0.6 × 1 to 10μm in size. The rods occasionally form branched filaments, but these can be readily disrupted.

The cell wall is rich in lipids, making the surface hydrophobic and the mycobacteria resistant to many disinfectants and common laboratory stains. Once stained, the rods also cannot be decolorized with acid solutions; hence the name acid-fastbacteria. Most mycobacteria divide slowly, and cultures require incubation for up to 8 weeks before growth is detected because the structure of the cell wall is complex and the organisms have fastidious growth requirements (Murray *et al*.,2013).

Growth is enhanced by 5 to 10% carbon dioxide but is still veryslow, with a mean generation time of 12 to 24 hours. The classic medium, Lowenstein–Jensen, contains homogenized egg in nutrient base with dyes to inhibit the growth of non-mycobacterial contaminants. The dry, rough, buff-colored colonies usually appear after 3 to 6 weeks of incubation (Sherri's *et al*.,2004).

1.2.8.3 Diseasetransmission:

The agent of tuberculosis is transmitted almost exclusively by fine droplets of respiratory mucus suspended in the air. The tubercle bacillus is very resistant and can survive for 8 months in fine aerosol particles. Although larger particles become trapped in the mucus and expelled, tinier ones can be inhaled into the bronchioles and alveoli. This effect is especially pronounced among people sharing closed, small rooms with limited access to sunlight and fresh air. Factors that significantly affect a person's susceptibility to tuberculosis are inadequate nutrition, debilitation of the immune system, poor access to medical care, lung damage, and genetics (Talaroand Chess, 2008).

1.2.8.4 Pathogenesis:

1.2.8.4.1 Primary Infection

The site of the initial infection is usually the lung,following the inhalation of bacilli. These bacilli are engulfed by alveolar macrophages in which they replicateto form the initial lesion. Some bacilli are carried

in phagocytic cells to the hilar lymph nodes where additional foci of infection develop. The initial focus of infection together with the enlarged hilar lymph nodes forms the primary complex. In addition, bacilliare seeded by further lymphatic and haematogenousdissemination in many organs and tissues, including other parts of the lung. During infection, antigens of *M. tuberculosis* are processed by antigen-presenting cells, activated by bacterial components termed adjuvants, and presented to antigen-specific T lymphocytes which undergo clonal proliferation. The activated T cells release cytokines, notably interferon-γ, which, together with calcitriol, activate macrophages and cause them to form a compact cluster, or granuloma, around the foci of infection ,These activated macrophages are termed epithelioid cellsbecause of their microscopically resemblance to epithelial cells. Some of them fuse to form multinucleate giant cells. The Center of the granuloma contains a mixture of necrotic tissue and dead macrophages, and, becauseof its cheese-like appearance and consistency, isreferred to as *caseation*.Activated human macrophages inhibit the replicationof the tubercle bacilli, but their ability to killingested bacilli is limited. Being metabolically veryactive, the macrophages in the granuloma consumeoxygen, and the resulting anoxia and acidosis in thecenter of the lesion probably kills most of the bacilli.

Granuloma formation is usually sufficient to limit the primary infection: the lesions become quiescent and surrounding fibroblasts produce dense scar tissue, which may become calcified. Programmed cell death (apoptosis) of bacteria-laden macrophages by cytotoxic T cells and natural killer (NK) cells contributes to protective immunity by generating a metabolic burst that kills tubercle bacilli (Greenwood *et al.*, 2012).

1.2.8.4.2 Secondary tuberculosis:

In about 10% of infected persons the primarytuberculosis reactivates to become an organ tuberculosis, either within months (5 %) or after a

number of years (5 %). Exogenous reinfection is rare in the populations of developed countries. Reactivation begins with acaseation necrosis in the center of the granulomas (also called tubercles) that may progress to cavitation (formation of caverns). Tissue destruction is caused by cytokines, among which tumor necrosis factor alpha (TNFa) appears to play an important role. This cytokine is also responsible for the cachexia associated with tuberculosis. Reactivation frequently stems from old foci in the lung apices. The body's immune defenses have a hard time containing necrotic tissue lesions in which large numbers of TB cells occur, the resulting lymphogenous or hematogenous dissemination may result in infection foci in other organs. Virtually all types of organs and tissues are at risk for this kind of secondary TB infection. Such infection courses are subsumed under the term extrapulmonary tuberculosis (Kayser*et al.*, 2005).

1.2.8.5 Clinical feature:

Primary tuberculosis is either asymptomatic or manifest only by fever and malaise. Radiographsmay show infiltrates in the mid-zones of the lung and enlarged draining lymph nodes in the area around the hilum. When these lymph nodesfibrose and sometimes calcify, they produce a characteristic picture (Ghon complex) on radiograph. In approximately 5% of patients, the primary disease is not controlled and merges into the reactivation type of tuberculosis, or it disseminates to many organs to produce active miliary tuberculosis. The latter may result from a necrotic tubercle eroding into a small blood vessel. In secondary TBCough is the universal symptom. It is initially dry, but as the disease progresses sputum is produced, which even later is mixed with blood (hemoptysis). Fever, malaise, fatigue, sweating, and weight loss all progress with continuing disease. Radiographically, infiltrates appearing in the apices of the lung coalesce to form cavities with progressive destruction of lung

tissue. Less commonly, reactivation tuberculosis can also occur in other organs, such as the kidneys, bones, lymph nodes, brain, meninges, bone marrow, and bowel. Disease at these sites ranges from a localized tumor-like granuloma (tuberculoma) to a fatal chronic meningitis. Untreated, the progressive cough, fever, and weight loss of pulmonary tuberculosis creates an internally consuming fire that usually takes 2 to 5 years to cause death. The course in AIDS and other CMI-compromised patients is more rapid (Sherri's *et al.,* 2004**).**

1.2.8.6 Laboratory Diagnosis:

Clinical diagnosis of tuberculosis traditionally includes some combinationof these techniques:

- tuberculin or immunologic testing,
- **.** roentgenography (X rays),
- direct identification of acid-fast bacilli (AFB) in sputum orsome other specimen, andcultural isolation and identification.

Final diagnosis of overt or latent TB cannot be made on a single test alone but requires an overall medical evaluation (Talaro and Chess**,** 2008).PCR and number of different rapid TB diagnostic methods havebeen introduced in recent years that require less time than the traditional methods, as Early-stage growth detection in liquid mediums involving identification of TB metabolic products with highly sensitive, semi-automated equipment which require one to three weeks(Kayser*et al.*,2005).

1.2.8.6.1 Specimens:

The most usual specimen for diagnosis of pulmonarytuberculosis is sputum but, if none is produced, bronchial washings, brushings or biopsies and early morning gastric aspirates (to harvest any bacilliswallowed overnight) may be examined. Tissue biopsies are

homogenized by grinding for microscopy and culture. Cerebrospinal fluid, pleural fluid, urine and other fluids are centrifuged and the deposits examined (Greenwood *et al.*, 2012).

1.2.8.6.2 Acid-Fast Staining:

Acid-fast staining of sputum or other specimens may be used to detect *Mycobacterium* , with several variations of the technique currently in use. The Ziehl-Neelsen stain produces bright red acid-fast bacilli (AFB) against a blue background. Fluorescence staining shows luminescent yellow-green bacilli against a dark background.The fluorescent acid-fast stain is becoming the method of choice because it is easier to read and provides a more striking contrast (Talaro and Chess**,** 2008).

1.2.8.6.3 Laboratory Cultivation and Identification:

Mycobacterium. *tuberculosis* infection is most accurately diagnosed by isolatingand identifying the causative agent in pure culture. Because of thespecialized expertise and technology required, this is not done bymost clinical laboratories as a general rule. Diagnosis that differentiates between *M. tuberculosis* and other mycobacteria must be accomplished as rapidly as possible so that appropriate treatment and isolation precautions can be instituted Cultures are incubated under varying temperature and lighting conditions to clarify thermal and pigmentation characteristics and are then observed for signs of growth. Several newer cultivation schemes have shortened the time to several days instead of the 6 to 8 weeks once necessary. Other identification techniques use DNA probes to detect specific genetic markers and can confirm positive specimens early in the infection. Rapid diagnosis is particularly important for public health and treatment considerations (Talaro and Chess**,** 2008).

1.2.8.7 Vaccination:

BCG vaccine contains a live attenuated mycobacteriumderived from *M. bovis*. It stimulates a protective immune response to *Mycobacterium*

tuberculosis, It is given as a single intradermal dose, a local reaction develops at the immunization site within 2–6 weeks, beginning as a small papule which increases in size, often ulcerates and gradually heals, leaving a small, 'punched out' scar (Bannister *et al*., 2006). BCG should never be given to persons known to be HIV-positive. Many attempts are currently being made to develop alternative vaccines,particularly non-viable subunit ones (Greenwood *et al*., 2012).

1.2.8.8 Treatment:

TB is treatable and curable disease. Active, drug-susceptible TB disease is treated with standard 6 months course of 4 antimicrobial drugs that are provided with information, supervision and support to the patient by a health worker or trained volunteer. without such support , treatment adherence can be difficult and the disease can spread. The vast majority of TB cases can be cured when medicine are provided and taken properly (WHO, 2017).

Drug resistance is avoided by a therapeutic regimen that combines at least two drugs selected from a list of 10, including isoniazid (INH), rifampin, ethambutol, streptomycin,pyrazinamide,thioacetazone, or para-aminosalicylic acid (PAS).The choice of drugs depends upon such considerations as effectiveness, adverse side effects, cost, and special medical problems of the patient. A one-pill regimen called Rifater(INH, rifampin, and pyrazinamide) is considered the best combination to effect cure and prevent resistance. If one combination is not working well because of toxicity, drug resistance, or hypersensitivity, a reasonably effective replacement is usually available. The presence of a negative culture or a gradual decrease in the number of AFB on a smear indicates success. However, a cure will not occur if the patient does not comply with drug protocols, which accounts for many relapses. Although it is essential to identify and treat people with active TB, it is equally

important to seek out and treat those in the early stages of infection or at high risk of becoming infected. Treatment groups are divided into tuberculin-positive “converters” who appear to have a latent infection, and tuberculin-negative people in high-risk groups such as the contacts of tubercular patients. The standard treatment is a daily dose of isoniazid for 9 months or rifampin for 4 months. In the hospital, the use of UV lamps in air conditioning systems and negative pressure rooms to isolate TBpatients can help control the spread of infection (Talaro and Chess.**,** 2008).

Previousstudies:**1.3.**

Bashir and his colleges (2014) conclude that thrombocytosis detected in 20% of PTB in their case control study in Port Sudan City which include 76% males and 24% females (Bashir *et al.*, 2014).

PTB patients Thrombocytosis also obtained by Mohamed (2013) in his case controlstudy in which he reported that platelet count was significantly increased (393.45 +/- 158.2) among PTB patients in Khartoum state (Mohamed, 2013).

Prolongation of PT and APTT and thrombocytosis among TB patients were reported by Eldourand his coworkers in 2014 in their case control study in North KordfanState in a case control study.

On the other hand **(**Kartaloglu *et al.*, 2000) conclude their case control study with significant prolongation of PT among 28 (56%) PTB patients with no significant prolongation in APTT.

However Wang and his team (2005) reported that TB can cause DIC, their study showed that 27 (3.2%) out of 833 patients with culture proven TB had tuberculosis induced DIC (Wang *et al.*, 2005) in their retrospective study in Taiwan.

1.3 Justification:

Tuberculosis is one of most common diseases worldwide**,** with high morbidity and mortality rates. About a third of the world's population is estimated to be infected with tubercle bacilli and hence at risk of developing active TB disease.

Various inflammatory cells, cytokines and mediators are involved in the formation of granulomatous lesions encountered in tuberculosis ,also some studies document that an increase in platelet counts in pulmonary and pleural tuberculosis (Kartaloglu*et al*., 2000). Immunecomplexes and many other factors elaborated in various infectious diseases are shown to induce pro-coagulant tissue factor (TF) expression in monocytes/macrophages and the endothelium, which under normal healthy state doesn't expressed TF **(** Eldour*et al*., 2014).

According to my search there is no studies done to demonstrate coagulation state of patients with TB infection in Khartoum state.so this study may highlight the relation between TB infection and coagulation parameters.

1.4 Objectives:

1.4.1 General objective:

To evaluate prothrombin time, activated partial thromboplastin time and INR among Pulmonary tuberculosis Patients in Khartoum state.

1.4.2 Specific objectives:

- To estimate PT,INR and APTT in active pulmonary tuberculosis patients and healthy one .

- To compare PT,INR and APTT of pulmonary tuberculosis patients with that of control.

-To detect correlation between PT, INR, APTT and other possible risk factor among TB patients.

-To detect correlation between PT, INR, APTT and gender.

1.5 Hypothesis:

Null Hypothesis: no significant difference between PT, APTT and INR of pulmonary tuberculosis patients and that of healthy one.

Alternative Hypothesis: PT, APTT and INR ofpulmonary tuberculosis patients are significantly differ than that of healthy one.

Chapter Two

Materials & Methods

Chapter Two

Materials and methods

2.1 Study Design:-

This was prospective case control and hospital based study.

2.2 Study Area and Duration:-

This study was done in Aboanga hospital in Khartoum state during the period from January to April 2017.

2.3 Study Population:-

Diagnosed active pulmonary tuberculosis patients attended to Aboanga Hospital was taken as cases and matched group of apparently healthy as controls after their verbal consent.

2.4 Inclusion Criteria:-

Cases included only fully diagnosed (by sputum cultivation)active PTB patients .

Control included only apparently healthy individual.

2.5 Exclusion Criteria:-

All non TB patients, non-fully diagnosed patients,patients on latent stage of disease and patients with history of bleeding or thrombosis abnormality was excluded from case group.

All individual that show any bleeding or thrombosis abnormality, pregnant women's and those who are under any treatment or suffer from inflammation was excluded from control group.

2.6 Sample Size:-

This study included 50 cases and 50 controls individuals .

2.7 Sampling:-

1.8 ml of venous blood to 0.2 ml of 3.2% tri sodium citrate was collected from each patient/control using disposable sterile syringe after dis infecting collection site with 70% alcohol, platelet poor plasma was prepared by centrifugation at 4000 rpm for 15 minute then PT and APTT test done within two hour of sample collection.

2.8 Data Collection:-

Data were collected using self-administered questionnaires. The questionnaires was specifically designed to collect demographic data information's about age, sex, smoking state and method by which patient diagnosed.

2.9Principles and Procedures:-

2.9.1 Principle of Coagulometer :

Photo-optical (turbidometric) coagulometer detect a change in plasma optical density (OD, transmittance) during clotting. Light of specified wave length passes throw plasma, and it is intensity (OD) is recorded by photo detector. The OD depends on the color and clarity of the sample and is established as the baseline. Formation of the fibrin strand causes light to scatter, allowing less to fall on the photo detector and thus generating an increase in OD. When the OD rise to predetermined variance from base line, the timer stops, indicating clot formation (www.clinicalgate.com).

2.9.2Principle of Prothrombin Time:

The PT test measures the clotting time of re calcified plasma in the presence of an optimal concentration of tissue extract (thromboplastin)

and indicates the overall efficiency of the extrinsic clotting system (Bain *et al*.,2011).

2.9.2.1 Test Procedure:

- Cuvettes were placed in incubation area for pre warming at 37 c for 3 minute at least.
- 100 ul of pre wormed (37c)control or patient PPP was dispensed in cuvette in incubation area.
- Then cuvettes transferred to test area and 200ul of well mixed calcified thromboplastin reagent were added to cuvette, the analyzer timer started automatically when reagent was added.
- When clot formed timer was stopped automatically as result of optical density changes, the analyzer is bi channel , get the mean of the two tested cuvettes and express it as PT on instrument display screen per seconds together with calculated INR .

2.9.2.2 Normal Values:

10-15 seconds (according to manufacturer).

2.9.3 Principle of Activated Partial Thromboplastin Time:

The test measures the clotting time of plasma after the activation of contact factors and the addition of phospholipid and CaCl2', but without added tissue thromboplastin, and so indicates the overall efficiency of the intrinsic pathway. To standardize the activation of contact factors, the plasma is first pre incubated for a set period with a contact activator such as kaolin, silica or ellagic acid (Bain *et al*., 2011)

2.9.3.1 Test Procedure:

- Cuvettes were placed in incubation area for pre warming at 37 c for 3 minute at least.

- 100 ul of pre wormed (37c)control or patient PPP was dispensed in cuvette in incubation area.
- 100 ul of cephalin/ kaolin mixture was added to each cuvette.
- After 3 minute incubation 100ul of calcium chloride were added to each cuvette after they transferred to test area.
- When clot formed timer were stopped automatically as result of optical density changes, the analyzer is bi channel , get the mean of the two tested cuvettes and express it as APTT on instrument display screen per seconds.

2.9.3.2 Normal Values:

28-40 seconds (according to manufacturer)

2.10 Ethical Considerations:-

Participants were informed verbally in their simple language about the research, its benefits and method of sample collection, then their approval taken.

2.11 Statistical analysis:-

The statistical analysis of the results was performed by using the Statistical Package for Social Sciences (SPSS) version 11.5 for windows version 7 using T-test for testing difference significance and Pearson correlation test (*r* value as the coefficient). *P* value ≤ 0.05 was considered statistically significant.

Chapter Three

Results

3. Results

This study was carried out in Khartoum state at Aboanga hospital during period from January to April 2017.

50 volunteer TB patients were enrolled in this study and matched group of apparently healthy control, percent and frequency of males and females among case group were78 % (39/50) and 22%(11/50) respectively (Figure 3.1), with mean age of 31.98 +/-10.7years.

44%(22/50) are smoker while 56%(28/50) are non-smoker (Table3.1).

Participated TB patients were classified according to age in to three groups (15-30), (31-45) and (46-60) years. The age group of (15-30) years was most frequent, while the least one was (46-60) years(Table3.2).

The results show that means of PT/INR showed statistically slight significant difference between case and control group while APTT reflect explicit significance difference (Table 3.3).

There was statistically no significant difference between means of measured parameter (PT, INR and APTT) among sex or smoking group(Table 3.4 and 3.5)

Finally there was weak positive correlation between PT/APTT and INR/APTT(Table 3.6)

Table 3.1: Frequency of smoking among cases group:

Smoking	Frequency	Percent
Yes	**22**	**44**
No	**28**	**56**
Total	**50**	**100**

Table 3.2: Age group distribution among TB patients:

Age group	Frequency	Percent %
15-30	24	48
31-45	20	40
46-60	6	12
Total	50	100

Table 3.3:Means ± SD and *p. values*of parameter among case and control group:

Parameter	Case	Control	*P. value*
PT	15.8 ± 2.8	14.9± 1.5	0.053
INR	1.2 ± 0.2	1.1 ± 0.1	0.052
APTT	46.2 ± 6.7	39.6 ± 4.6	0.000

Table 3.4: Means and *p. values* of parameter among sex group of TB patients:

Parameter	Sex	Mean ± SD	*p. value*
PT	Male	15.6 ±2.7	0.231
	Female	16.7± 3.1	
INR	Male	1.1 ± 0.2	0.215
	Female	1.2 ± 0.3	
APTT	Male	45.9± 6.4	0.568
	Female	47.2 ± 7.6	

Table 3.5: Means and *p. values* of parameter among smoking group of TB patients:

Parameter	Smoker	Mean ± SD	*p. value*
PT	Yes	16.1±3.4	0.518
	No	15.6± 2.4	
INR	Yes	1.2± 0.3	0.556
	No	1.1± 0.2	
APTT	Yes	45.7±6.3	0.633
	No	46.6± 6.9	

Table 3.6: Correlation between PT / APTT and INR/APTT among case group.

Parameter A	Parameter B	*P. value*	r Value
PT	APTT	0.035	0.300
INR	APTT	0.041	0.291

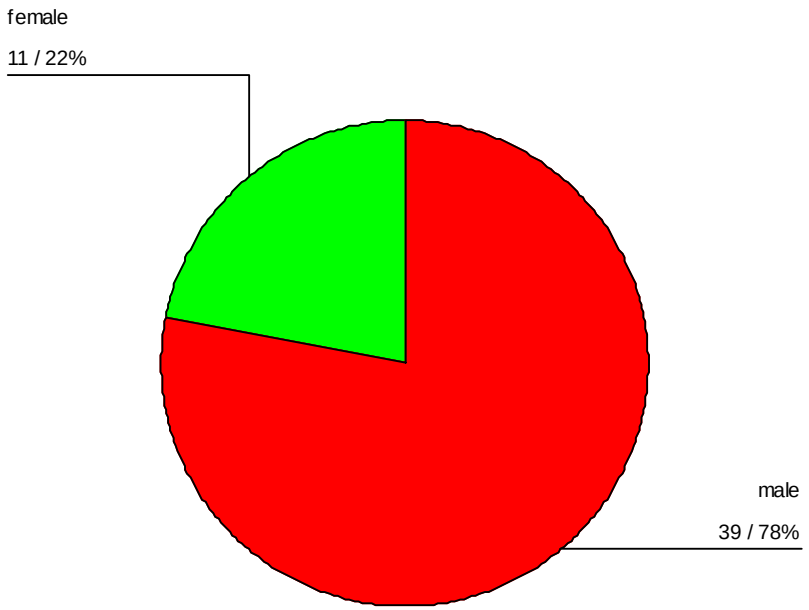

Figure 3.1: Sex distribution among PTB patients

Chapter Four

Discussion, Conclusion and Recommendations

4.1 Discussion

This is a case control study conducted in Aboangahospital during the period from January to April 2017. The study performed to find out subsequent effect of active pulmonary tuberculosis on coagulation to tries to establish policies to be considered in the management of patients with PTB. It include 50 PTB patients and 50 age and sex matched group of apparently healthy control, age of participated patient range from 16-58 years with mean of 31.98 +/- 10.7 years.

The present study reflect that most of cases members are males(78%) rather than female (22%) this agree with studies of Kartaloglu and his coworkers whom report that54 male and 6 female in their study *Parameters Of Blood Coagulation In Patients With Pulmonary Tuberculosis(*Kartaloglu*et al.*, 2000) On the other hand in the present study most of PTB patients are nonsmokers (56%) rather than smokers (44%).

In the present study there is significant prolongation in PT/ INR and APTT in cases when compared to control group (*p. value* ≤ 0.05).In my opinion *invivo*initiation coagulation resulting from cell injury that occur as result of overlapping pf macrophages and epithelioid cells in order to kill invading mycobacterium, which result in local tissue hypoxia that end with cell injury that indicated also by blood that observed with the cough, so collagen and tissue factor become exposed and secondary coagulation initiated resulting in thrombosis. Furthermore, this prolongation may be due to malfunctioning of factor/ factors substance that associated in maintain normal hemostasis as subsequent effect of PTB infection.

My results werefully agree with study of Kutial and his colleges in the study of haematology and haemostasis parameters and hypercoagulable state in tuberculosis patients in north india and the outcome with anti-tubercular therapy in which they report that PT and APTT were significantly high (kuital*et al.*,2017) also present study is with full agreement with study ofBlood Coagulation Changes among Sudanese Patients with Pulmonary Tuberculosis in which Eldour and his colleges report that PTB is associated with prolongation of PT and APTT (Eldour*et al.*, 2014). Partial agreement of present study with Kartaloglu and his coworkers in their study in which they report that PT increased significantly in 28 patients (56 %) with pulmonary tuberculosis while there was no significant prolongation in APTT (Kartaloglu *et al.*, 2000).

Because of the association between inflammation and hemostatic changes that can result in a hyper-coagulable state . However, infection triggers both pro-inflammatory and anti-inflammatory host responses, the magnitude of which depends on multiple factors, including pathogen virulence, and the immune response after recognition of danger signals derived from microorganisms. This is further exploring the role the cytokine response, the coagulation cascade and their multidirectional interactions . However, many theories have been proposed for these blood coagulation disorders. Systemic inflammation results in activation of coagulation, due to tissue factor-mediated thrombin generation, down regulation of physiological anticoagulant mechanisms, and inhibition of fibrinolysis (Eldour*et al.*, 2014).

4.2 Conclusion

- PT/INR and APTT are prolonged in PTB patients.
- There is no significant difference in PT, INR and APTT results between smoker and non smoker or males and females among active PTB patients.

4.3 Recommendations

- Further studies should be done to determine the cause of prolongation in PT and APTT**.**
- Prothrombin time /INR and activated partial thromboplastin time should be done as follow up for active pulmonary TB patients to avoid risk of hemostatic changes**.**

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Appendices

Appendix (I)

materials and Equipment's of PT and APTT test:

- Pooled normal plasma.
- PPP under test.
- PT reagent "Calcified thromboplastin" (rabbit :brain extract of thromboplastin , calcium chloride 0.25M ,buffer and stabilizer).
- APTT reagent (kaolin cephalin with phospholipid , buffer and preservative).
- Calcium chloride (0.25M).
- Coagulation analyzer.
- Calibrated pipette.
- Pipette tips.
- Small cuvettes.
- Racks

Appendix (II)

Sudan University of Science & Technology

Collage of graduate studies

Measurement of Prothrombin Time and Activated Partial Thromboplastin Time in TB Patients

Questionnaire

Patient ID Number:…….

Age: |___| years

Gender: Male { } Female{ }

Smoker: Yes { } No { }

Do you have pervious Bleeding or Thrombosis?

Yes{ } No{ }

If your family have history of Bleeding or Thrombosis?

Yes{ } No{ }

Method by which TB diagnosed ?

Results:

PT:……..second

INR:……

APTT:…….second

Date:……

Appendix (III)

Diagon diatimer-2 (right)