# PREVALENCE AND IMPLICATIONS OF THE LUPUS ANTICOAGULANT IN PATIENTS WITH END STAGE RENAL DISEASE

*Thesis Submitted in Partial Fulfillment of the M.D. Degree*

*in*

*INTERNAL MEDICINE*



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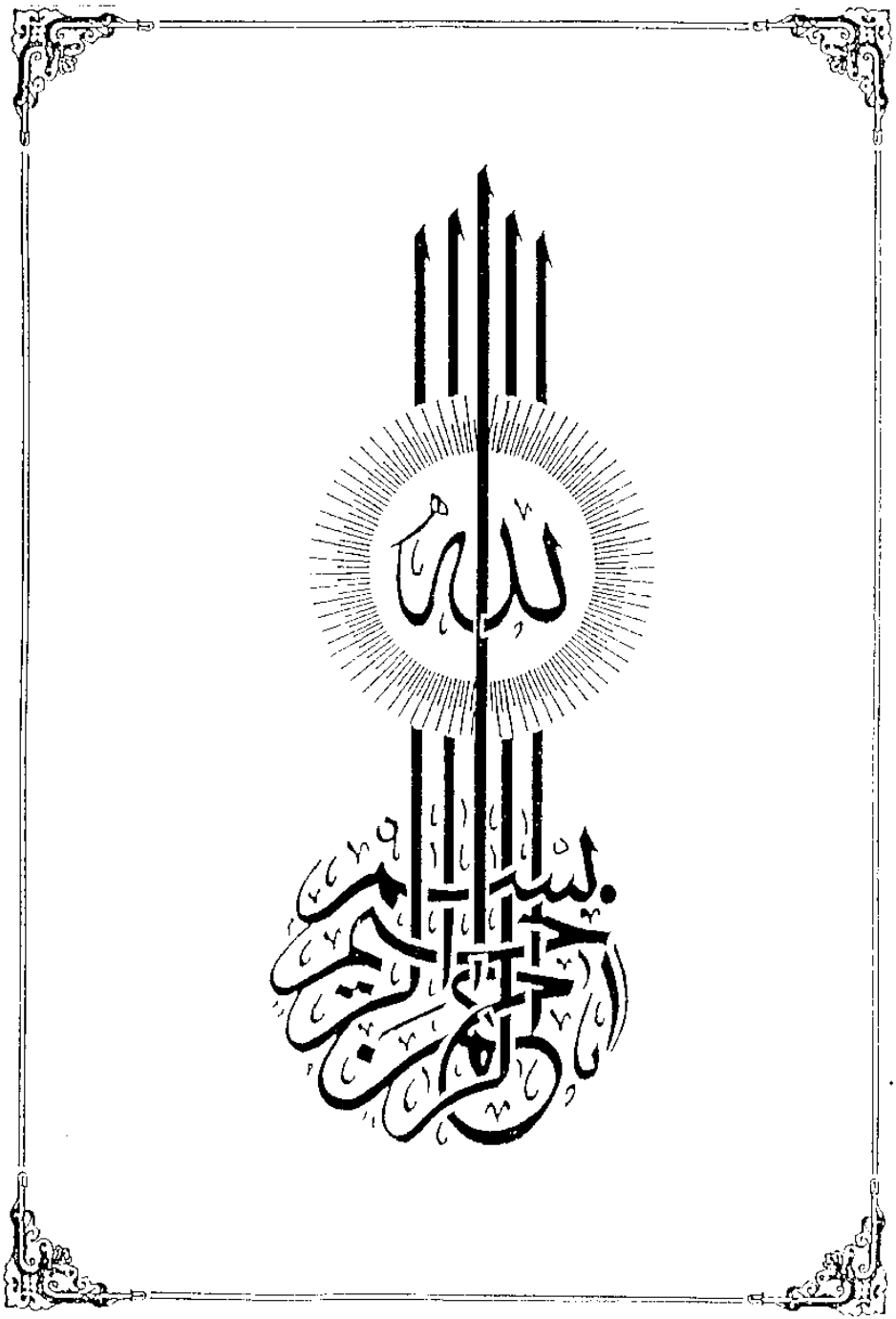


LIST OF
ABBREVIATIONS

# LIST OF ABBREVIATION

| | | |
|---|---|---|
| **a.c.l.** | : | Anti - cardiolipins. |
| **L.A.** | : | Lupus anticoagulant. |
| **a.P.T.T** | : | Activated partial thromboplastin time |
| **B.T.I.T.** | : | Blood thromboplastin inhibition test |
| **T.T.I.T.** | : | Tissue thromboplastin inhibition test |
| **D.R.V.V.T.** | : | Dilute Russel viper venom time. |
| **S.L.E** | : | Systemic lupus erythematosus. |
| **A.N.A.** | : | Anti-nuclear antibody. |
| **V.D.R.L.** | : | Venereal Disease Research Laboratory. |
| **E.S.R.D.** | : | End stage renal disease. |
| **A.D.P.** | : | Adenine diphosphate. |
| **TxA2** | : | Thromboxane $A_2$ |
| **PGI2** | : | Prostaglandin $I_2$ |
| **K.C.C.T.** | : | Kaolin cephalin clotting time |
| **T.I.A.** | : | Transient ischemic attack. |

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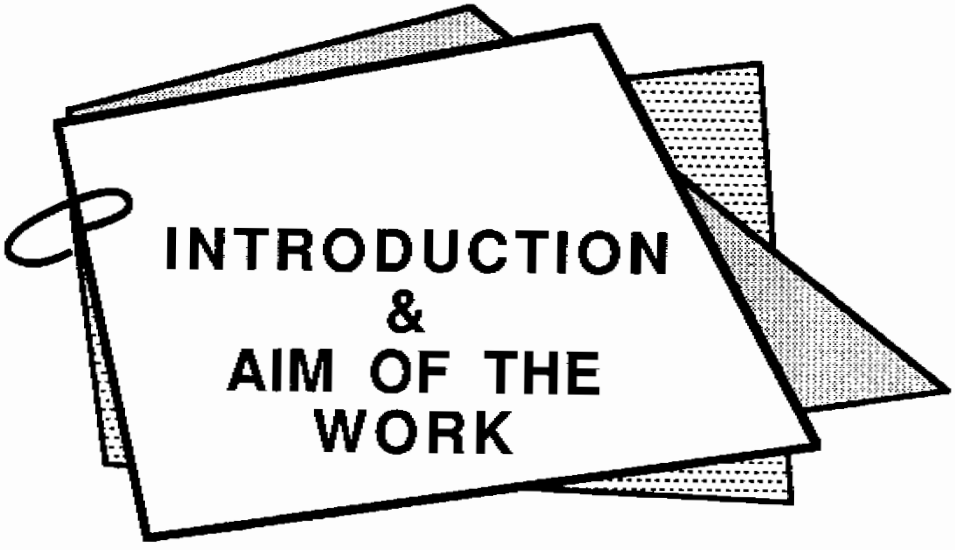
INTRODUCTION
&
AIM OF THE
WORK

# INTRODUCTION AND AIM OF THE WORK

The lupus anticoagulant first described by ***Conley and Hartman in 1952,*** is a spontaneously acquired inhibitor of blood coagulation that interferes with the activation of prothrombin by the activator complex (Factor Xa, V, calcium and phospholipids) ***(Feinstein et al., 1972).*** This inhibitor, an immunoglobulin of the IgG or IgM class appears mostly in the plasma of patients with auto-immune disorders including systemic lupus erythematosus (SLE), but has been described in patients with diseases not directly associated with the immune system. ***(Schleider et al., 1976).*** Recently, it appeared that the most frequent clinical manifestations observed in those patients who have the lupus anticoagulant is an increased tendency to display thrombotic complications ***(Mueh et al., 1980).*** Whereas a bleeding tendency, caused by several abnormalities in platelet function is well known in the uremic state, arteriopathies, and thrombotic disorders are frequently seen among the hemodialysis patients along with thrombotic prone coagulation disorders. ***(Linder et al., 1974).*** In spite of the growing interest in the studying of the lupus anticoagulant, and its relation to thromboembolism in various immunologic and non-immunologic disorders, its presence in patients with end stage renal disease (ESRD) is

reported in only very few reports previously. The purpose of our work is to determine the prevalence of lupus anticoagulant in patients with ESRD, whether or not treated with hemodialysis, and to determine whether these patients who have the lupus anticoagulant are at increased risk of thromboembolism.


REVIEW OF
LITERATURE

# OVERVIEW OF THE THROMBOTIC PROCESS

Thrombi may form in any part of the cardiovascular system including veins, arteries, the heart and the microcirculation. The complications of thrombosis are due to either local obstruction of the vessel or distant embolization. Most venous thrombi occur in the lower limbs. They are usually silent, but produce symptoms if they cause local inflammation of the vessel wall or obstruction to flow or if they embolize into the pulmonary circulation. Arterial thrombi usually occur in association with pre-existing vascular disease, the most common of which is atherosclerosis. They frequently produce tissue ischaemia either by obstructing flow or by embolizing into the distal microcirculation. Intracardiac thrombi usually form on damaged valves or endocardium or prosthetic valves. They are always asymptomatic when confined to the heart but may produce serious complications if they embolize into systemic circulation. Disseminated thrombosis of the microcirculation is a complication of disseminated intravascular coagulation or disseminated platelet aggregation. This may be complicated by ischemic necrosis and by a hemorrhagic disorder due to consumption of platelets and clotting factors. Thrombi are composed of fibrin and blood cells. The relative proportion of one type of cell to another

and to fibrin is influenced by hemodynamic factors, and therefore the proportions differ in arterial and venous thrombosis ***(Freiman et al., 1982)***. Arterial thrombi form under conditions of high flow and are composed mainly of platelet aggregates held together by fibrin strands ***(Baumgartner, 1973)***. Venous thrombi form in areas of stasis and are composed of red cells with a large amount of interspersed fibrin in relatively fewer platelets. When thrombi form in areas of slow to moderate flow, they are composed of a mixture of red cells, platelets and fibrin and are known as mixed platelet fibrin thrombi ***(Jorgensen et al., 1967)***. Thrombi undergo constant structural change as they age leucocytosis are attracted by chemotactic factors released from aggregated platelets and become incorporated into the thrombi ***(Hirsh et al., 1974)***. The aggregated platelets swell and undergo autolysis and are gradually replaced by fibrin which is eventually digested by proteolytic enzymes released from the leucocytes and by plasma fibrinolytic enzymes ***(Collen, 1980)***. Thrombosis usually occurs when there is breakdown in the balance between thromboegnic factors and protective mechanisms ***(Hirsh et al., 1974)***.

## The Thrombogenic Factors are:

- Damage to the vessel wall.
- Stimulation of platelet aggregation
- Activation of blood coagulation
- Stasis

## The Protective Mechanisms are:

- The nonthrombogenic properties of the intact endothelium
- Neutralization of the activated coagulation factors by naturally occuring protease inhibitors.
- Dilution of activated clotting factors disruption of platelet aggregates by blood flow.
- Activation of activated coagulation factors by the liver
- The firbinolytic system.

## Thrombogenic Factors:

*Damage to the vessel wall:*

When a vessel is damaged, there is endothelial loss and exposure of the subendothelium to both platelets and the blood coagulation factors ***(Mustard et al., 1982).*** Vessel damage may be caused by direct physical injury and may also be mediated by immune complexes, viruses or bacteria, hemodynamic stress, tobacco products, high blood, cholesterol and enzymes released from platelets and leucocytes in inflammatory states ***(Mustard et al., 1982).*** Vascular damage and disturbed blood flow, two important factors predisposing to arterial thrombosis are mutually reinforcing; each contributes to the genesis of the other. When platelets interact with exposed subendothelial and flow is disturbed, they adhere, aggregate and form small

mural thrombi that are stabilized by fibrin. These mural thrombi can produce major complications if they obstruct an artery of if they embolize into the distal microcirculation and produce focal cell damage ***(Mason et al., 1976)***.

## The Role of Platelet Interactions in Thrombosis:

### 1. Platelet Adhesion:

Platelets do not adhere to normal endothelium but adhere to basement membrane and collagen, which is exposed when there is a break in the endothelial lining of blood vessels ***(Baumgartner et al., 1971)***. Platelet adhesion to subendothelial collagen requires Von Willebrand factor, which promotes platelet adhesion by binding to a glycoprotein receptor on the platelet surface ***(Caen et al., 1976)***. Defective adhesion occurs when this platelet membrane glycoprotein receptor is absent (Bernard - Soulier Syndrome) or if Von-willebrand factor is defective or deficient in the plasma as occurs in Von Willebrand disease ***(Caen et al., 1976)***.

### 2. Platelet Release Reaction:

A number of aggregating agents including collagen, thrombin, epinephrin and thromboxane $A_2$ (itself a platelet product) cause platelets to secrete their granular contents. ***(Holmsen, 1982)***. Platelets contain several kinds of secretory granules. When relatively weak stimuli e.g.: Dilute

suspensions of collagen are used, release of the contents of the dense granules predominates, while with stronger stimuli e.g. thrombin, the contents of "α- granules" are also released ***(Holmsen, 1982).***

"The dense granules" contain serotonin and adenosine diphosphate, and the "α- granules" contain the platelet specific proteins, platelet factor 4, "β- thromboglobulin, platelet derived growth-promoting factor, and, a variety of other proteins including fibrinogen, factor V, Von Willebrand factor, high molecular weight kininogen "α- antitrypsin and, "$\alpha_2$- macroglobulin. Release inducing agents also activate the platelet prostaglandin synthetic pathway ***(Kaplan et al., 1979).***

**3. Platelet Aggregation:**

Platelet aggregation can be induced by several stimuli, including adenosine diphosphate, collagen, thrombin, thromboxane $A_2$, and epinephrine ***(Packman, 1976).*** Platelet aggregation requires a platelet membrane glycoprotein receptor for fibrinogen which is lacking in the rare congenital disorder known as thrombosthenia and is normally involved in calcium dependent interplatelet bridging by fibrinogen ***(Bennett, Vilaire, 1979).*** This bridging reaction may also involve the "α- platelet granules' proteins: fibronectin and thrombospondin ***(Ginsberg et al., 1980).*** The binding of fibrinogen to a platelet membrane receptor is a pre-requisite for