PIATELETS AGGREGATION IN UNCONTROLLED DIABETES MELLITUS

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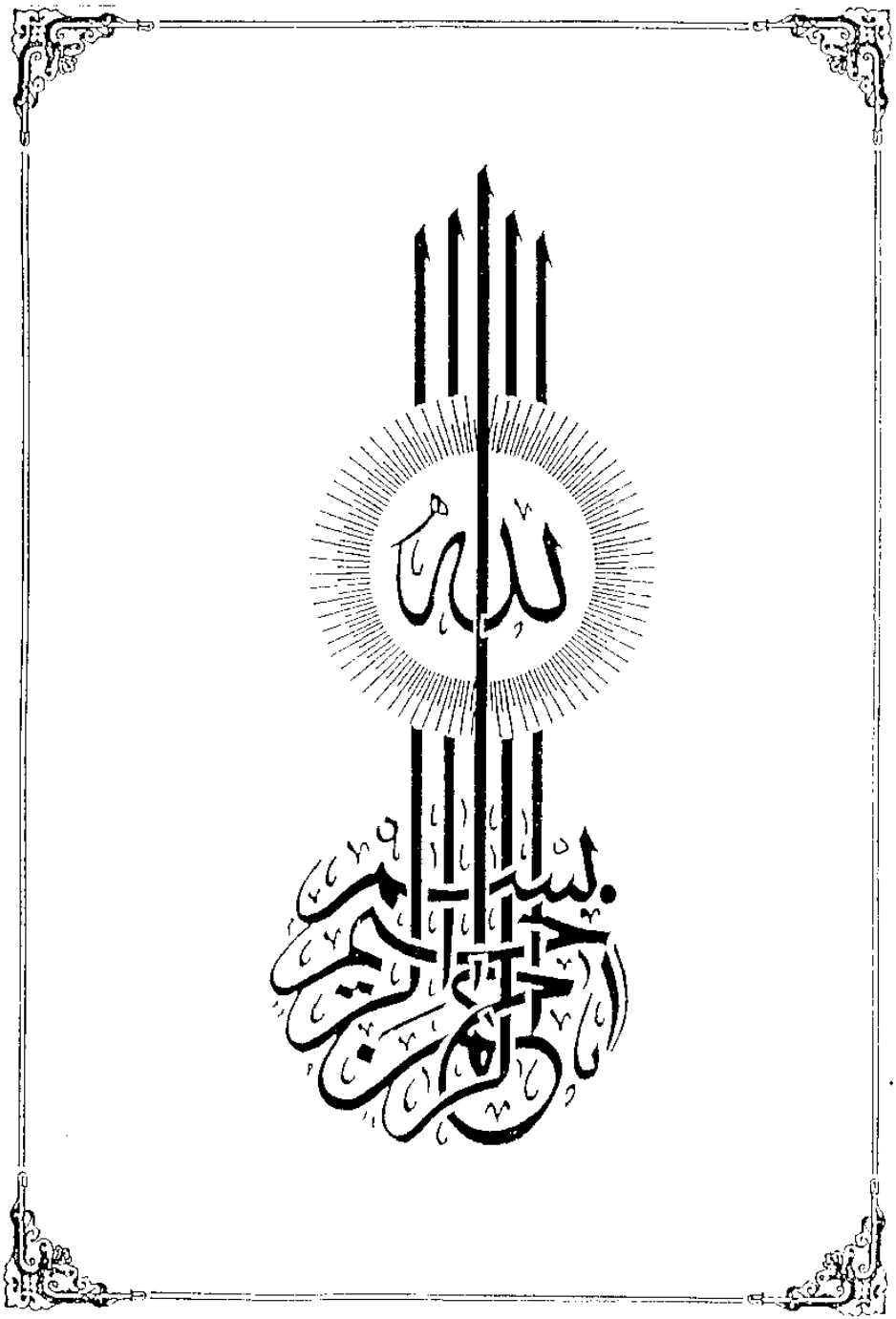

C O N T E N T S

INTRODUCTION

and

AIM OF THE WORK

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Patients with Diabetes mellitus are at increased risk for vascular disease. This was suspected to be due to increased circulating platelets aggregates in such patients (Davis 1982). Sagel (1975) has also reported that the platelets sensitivity to aggregating agents was most marked in frank diabetics, intermediate in latent diabetes and least in prediabetics.

They concluded that platelets aggregation may be involved in the genesis of diabetic microangiopathy More recently Davis (1982) recorded a significant decrease in platelets aggregation ratio of the juvenile-onset diabetics and the poorly controlled adult- onset diabetics.

Controversy is still present as regarding the correlation between metabolic changes of diabetic patients and their increased platelets aggregation.

Many anthors reported a correlation between increased platelets aggregation and increased level of blood lipids (Micic 1978 and Davis, 1983).

However, others found a correlation between increased platelets aggregation and levels of glycosylated haemoglobin(HbA_{1c})(Dettoni, 1983).

The level the glycosylated haemoglobin (HbA_1) was found by many workers to correlate significantly with the degree of hyperglycaemia which exists over long periods (Palusen, 1973; Ditzel, 1978; Coller, 1978 and Widness, 1980) thus HbA_1 measurement is considered an objective method to assess the state of diabetic control (Gonen, 1977). Taken together, these studies, it is thought that study of the platelets aggregation in diabetes mellitus is of prime importance.

Diabetic patients both insulin dependent and non insulin dependents and prediabetic ones are selected for this work.The status of glucose metabolism will be assessed by determination of glycorylated haemoglebin levels.

A correlation between the defect in platelets aggregation and the level of glycosylated haemoglobin (A_{1c}) and total serum lipids will be attempted.

REVIEW OF LITERATURE

Chapter (1)

The Platelets

Introduction

Platelets or thrombocytes are of much greater importance and interest than their insignificant appearance. They play an important role at all the stages of haemostasis and they are active in maintaining the integrity of endothelium of blood vessels (Thompson, 1977).

Formation

Platelets are derived from megakaryocytes in the bone marrow. These are large giant cells with large lobed ring shaped nuclei and basophilic granular cytoplasm. The megakaryocytes are descended from megakargoblasts which in turn originated as independent cell line from uncomitted multipotent stem cells.

Pseudopodia are said to be detached from the cytoplasm of the megakaryorytes through the walls of blood sinusoids then circulate in the blood as platelets, although some haematologists think that platelets are derived from the extruded nuclei of red blood corpuscles. (Thompson, 1977).

Morphology and ultrastructure

Platelets are non- nucleated bodies of discoid shape which measures an average of 3 um in length and 1 um in thickness (Thompson 1977) using the light microscope the platelet appears to be simple with transparent cytoplasm (hyalo plasm) and a central darkly stained granular area (Chamarin 1976).

While using the electron microscope their structure appear to be more complex where the platelet can be divided into three zones: a peripheral zone containing platelet membranes , an internediate soft gel zone containing microfilaments resembling actin and myosin of smooth muscle cells and an inner organelle zone containing the platelets organelles (White, 1971).

The organelle zone consists of platelet granules, dense bodies, mitochondria, golgi zone, dense tubular system and glycogen granules (white , 1971).

The peripheral zone is the site of platelets adhesion and aggregation (O'Brien, 1970).

While the soft gel zone contains a contractile protein similar to smooth muscle proteins and is responsible for platelets contraction and clot retraction. (thompsoh, 1977).

Many authors noted the presence of an open system of channels in the platelet hyoloplosm. This system may be the route by which the products of platelet secretion reach the cell exterior as well as a pathway for the uptake of plasma substances to the platelet organelles (Wlite, 1970).

Platelet membranes

The platelet membranesare vital structure containing glycoprotein receptors which is acted upon by Von willebrand factor secreted by endothelium of blood vessles, thus initiate both platelets adhesion and aggregation. (Lubetzki, 1982).

It was found that the platelet membrane is composed of lipids (35%), proteins (57%) and Carbohydrate (8%) as glycoproteins, and glycolipids (Barber , 1970).

It appears that the cytoplasm of the unstimulated (Unactivated) platelet is surrounded by a plasma membrane which contains phospholipids in a bilayer pattern (Shattil and Bennet 1980).

This protein content of the platelet membranes is embedded within a fluid lipid bilayer (the phospholipid bilayer).

This membrane protein receives the message that vascular damage has occured and thus initiates the platelet functions. (Shattil and Bennet, 1980).

alpha and gamma granules

The storage granules of the platelets are heterogenous in content and morphology.

They can be classified into various types, one of the most important of them are the gamma granules or the electron dense granules, which contain the metabolically inactive storage form of ADP as well as serotonin and the majority of the platelet calcium (Shattil and Bennet, 1980).

Other important granules type is the alpha gramules which contain fibrinogen, a platelet derived growth factor, the platelet specitic proteins, platelet factor 4 and B-thromboglobulin. A third type of granules also exist which contain the lysosomal enzymes. (Holmesen, 1979).

Platelet adhesion

The adhesion of platelets to the sites of vascular injury is the initial event in the formation of the platelet plug.

It is the disruption of the vascular lining that initiates platelet adhesion to the underlying collagen, microfibrils and the subendothelial basement membrane (white, 1971).

Normally the vascular endothelial lining is inert with respect to the platelets. Recently it was discovered that the endothelial cells produce a potent platelet- inhibitery prostaglandin called prostacycline (PGI_2) and it is suggested that the continuous production of this prostacycline is responsible for the prevention of platelets adhesion to endothelium of the blood vessels (Moncade, 1978).

Platelets aggregation

After the adhesion of platelets to the injured vessel wall, they aggregate to each other and so forms clumps and eventually a hemostatic plug (Thompson, 1977).

Platelets when activated by ADP, thrombin or arachidonic acid they aggregate together.

If the stimulus is weak there will be only what is called first or primary - phase aggregation which is reversible by a process called disaggregation but if

the stimulus, also called the aggregating agent, is adequate then platelets will be stimulated to release their intracellular contents of ADP, serotonin and calcium and these substances will aggregate platelets together in what is called secondary-phase aggregation which is an irreversible event (Bern 1978).

It has been also suggested that platelets aggregation may be initiated by ADP derived from disrupted erythrocytes or extravascular tissues giving another sequence which is: aggregation by exogenous ADP - release reaction by the platelets - aggregation by the ADP released from platelets and this sequence may also play a role in mediating the primary arrest of bleeding. Thus the term primary or first - phase aggregation refers to the direct aggregation of platelets by ADP and other substances such as epinephrine, serotonin and thrombin derived from sources other than the platelets contents. While aggregation mediated through the relase of platelets ADP is referred to as the second -phase aggregation(Weiss 1975). In 1977, Charo defined two types of platelets activation and secretion, the first is that type of platelets secretion which begins after platelets aggregation and here platelets secretion of their contents is

dependent upon the aggregation and is referred to as aggregation-mediated platelets activation, this type is inhibited by indomethacin.

The other type is when secretion begins at the same time as the aggregation and he believed that secretion here can occur even in the absence of aggregation, this is referred to as directly induced- platelet activation and this type of activation can not be blocked by indomethacin. Thus secretion and second-phase aggregation appear to be parallel events with little or no evidence that second-phase aggreagation being a consequence of secretion as was usually described before.

Platelets activation and Secretion

(Release reaction)

Following platelets adhesion to vessel wall , the platelets are stimulated by thrombin or ADP derived from disrupted RBCSand extavascular tissues, some platelets in response aggregate while others undergo the release reaction (Shattil and Bennet, 1980).

The substances secreted by platelets are those found in their granules mainly ADP, while contents of platelets membranes, cytoplasm and mitochondria are retained, this process is named the release reaction.