Platelet Abnormalities in Diabetes Mellitus*

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ABSTRACT

Patients with diabetes mellitus have an increased risk of thrombosis and accelerated atherogenesis. Increased platelet adhesion and aggregation are noted in vitro. This paper reviews known platelet abnormalities found in patients with diabetes mellitus (DM) and examines the pathophysiology associated with these abnormalities. Four general platelet regions or functional units can be involved in aberrant chemistry, structure and/or function. These include (1) the membrane, (2) granules, (3) intermediary metabolism, and (4) other factors and/or platelet responses to various substances. In regard to the abnormalities of the membrane, there is an increased binding of fibrinogen in diabetic rats and increased membrane rigidity. There are increases in glycoprotein Ib and glycoprotein IIb/IIIa. Related to granule function, increased levels of plasma serotonin, histamine and beta thromboglobulin are found. Alterations of intermediary metabolism involving the prostaglandin pathways, arachidonic acid, Vitamin E, and lipids have been reported. Other factors which are not well characterized include abnormalities of stem cell response to growth factors and thrombopoiesis, as noted indirectly through alterations of platelet volumes. It is proposed that these platelet abnormalities result in increased thrombosis and/or an acceleration of the atherosclerotic process in at least some patients with diabetes mellitus.

Introduction

A variety of platelet abnormalities in diabetes mellitus has been reported. These changes are related to various functions or regions of the platelets and include: (1) the membrane, (2) granules, (3) intermediary metabolism, and (4) platelet responses to various substances and other factors. An increased sensitivity to platelet aggregating agents has been shown in a number of studies. Enhanced platelet adhesion to endothelial surfaces has been postulated. These effects have been noted in vitro, and it has been proposed that the abnormalities in platelet function and an association with endothelial alterations in diabetes mellitus may be a cause for the accelerated atherogenesis present in patients with diabetes mellitus. The objectives of
this study are (1) to review the platelet abnormalities in diabetes mellitus which have been described, and (2) to examine some of the pathophysiologic and biochemical associations of platelet abnormalities in diabetes mellitus (PADM) and relate this to the accelerated atherosclerosis in diabetes mellitus.

Methods

Selected literature related to abnormalities of platelet aggregation and adhesion in diabetes mellitus and the possible relationship to atherosclerosis were reviewed and evaluated.

Results

Diabetic platelets show an increased sensitivity to adenosine-diphosphate (ADP). This appears to be related to an increased binding of fibrinogen by those platelets. There is an increase in Vitamin E metabolism in diabetes mellitus which results in decreased aggregation of ADP and an increase in prostaglandin I\(_2\) (PGI\(_2\)). Prostaglandin F\(_2\) (PGF\(_2\)) is also noted to be increased. There is a decrease in platelet membrane fluidity and other not well-quantitated membrane changes which may be associated with the abnormal function. Polyphosphoinositide turnover is increased. G-Protein and adenylate cyclase activity are increased.

Diabetic platelets are noted to have an increased aggregability when incubated with thrombin, collagen, and arachidonic acid materials. This has been noted to be associated with a decrease in cyclic adenosinemonophosphate (cAMP), increased thromboxane B\(_2\) (TXB\(_2\)), and increased thromboxane A\(_2\) (TXA\(_2\)). These changes may be related to alterations in glycoproteins, particularly glycoprotein Ib (GPIb) and glycoprotein IIb/IIIa. Increased levels of von Willebrand's factor have been noted and correlated with elevated levels of hemoglobin A\(_1\)C in some studies. The outcome of these factors is an increase in platelet adhesiveness and platelet aggregation.

Abnormalities of calcium, magnesium, and sodium transport have been noted, but whether these are a cause or effect of platelet abnormalities seen in diabetes mellitus remains unanswered. There is increased binding of angiotensin II to diabetic platelets. Some authors have proposed that there is an interaction of immune globulins and/or complexes that may contribute to the platelet abnormalities in diabetes mellitus. Plasma levels of beta thromboglobulin have been noted to be increased, while there is an apparent decrease in platelet-derived growth factors in platelets of patients with insulin-dependent diabetes mellitus. This suggests that there is an increased release of platelet derived growth factor, and this may play a role in self-proliferation of diabetic angiopathy.

The question as to whether or not glucose control can result in improved platelet function is less well documented. Rigid glycemic control has been reported to result in improved platelet aggregation in response to PGI\(_2\) and enhanced TXB\(_2\) synthesis. Abnormalities such as possible impaired thrombopoiesis as measured by altered platelet volume in patients with diabetes mellitus do not seem to be responsive to control of glucose levels. Colwell reviews the role of gliclazide as a treatment for diabetes mellitus and its role on platelet function. There appears to be enhanced platelet function with reduced adhesiveness and aggregation when there is good control of hyperglycemia through the use of this oral agent. Other abnormalities of platelet function which have been recorded include increased sensitivity of platelets to thrombin binding in diabetic rats, platelet hyperaggregation, and hypersecretion of fibronecin in peripheral vascular disease of diabetic patients with microangiopathy, increased plasma serotonin, and increased histamine levels which are
hypothesized to contribute to increased endothelial permeability and the increased vascular abnormalities seen in diabetics (figure 1).

**Discussion**

A variety of functional abnormalities of platelets have been described in the literature. These include glycoprotein, receptor site, receptor binding, secretory functions, and metabolic and catabolic functions of the platelets. These abnormalities have been found in patients with insulin and non-insulin dependent diabetes mellitus. Experimental studies demonstrate the changes but are unable to give a definitive answer as to whether glycemic control can reverse some or all of these abnormalities.

Membrane abnormalities that have been noted include alterations in glycoproteins. Glycoprotein Ib is known to interact with von Willebrand’s factor to result in adherence of platelets to the subendothelium. The changes in the von Willebrand’s factor have been correlated with elevated levels of hemoglobin A1C and may indicate that diabetics who are in poor control will have a greater probability of thrombosis. Many platelet agonists, including adenosine diphosphate (ADP), thrombin, epinephrine, collagen, and arachidonic acid, are known to have specific receptors on the platelet membrane. The demonstration that patients with diabetes mellitus have an increased aggregability when incubated with these agonists indicates the potential for increased platelet adhesiveness and platelet aggregation.

The agonist-receptor interaction results in an increased cytoplasmic calcium ion concentration which is associated with a change in platelet shape. Calcium and magnesium concentration changes activate contractile mechanisms, resulting in fusion of the platelet granules with the platelet plasma membrane. Thromboxane A2 is formed and is an important intermediate step in successful granule release. The increased levels of TxA2 as well as increased levels of von Willebrand’s factor, fibrinogen, factor V, platelet factor IV, and beta thromboglobulin from the alpha granules all could be factors related to the acquired platelet defect in diabetes. The delta granules of platelets, which normally contain serotonin, adenosine triphosphate (ATP), pyrophosphate, and calcium, are all known to be present or have been recognized experimentally to be present in increased quantities, possibly indicating additional relationships to a predisposition for thrombus formation. The intermediary metabolic pathways altered to result in the increase or decrease in a variety of chemicals, membrane receptor sites or granule contents, have not been completely elucidated.

The interaction of the platelet surface glycoproteins IIb/IIIa complex with fibrinogen is noted to be abnormal and may result in increased aggregation of

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<td>Decreased magnesium</td>
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<td>Increased Alpha components:</td>
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**Figure 1.** Platelet abnormalities in diabetes mellitus.
the platelets. Not well explained is how alterations in the platelet membrane may affect the interactions with certain coagulation proteins, such as factor Xa or factor Va, the complex of which activates prothrombin to thrombin. The role of platelet-derived growth factor on endothelial proliferation suggests certain theoretical aspects of endothelial and platelet interactions. The effect of abnormal platelet function in diabetes as part of an hypothesized feedback mechanism for a thrombocyte stimulating hormone or a variety of interleukins, particularly interleukin 6 which may have an affect on platelet production, is only now being investigated.

Many of the alterations, such as increased platelet derived growth factor, increased histamine release, and associated endothelial changes could result in acceleration of the atherosclerotic process.

Conclusion

Many patients with diabetes mellitus develop abnormal platelet functions. Some of these abnormalities are at least in part related to glycemic control. The major abnormalities that are seen are increased aggregation and adhesion of platelets. There are multiple associated abnormalities of intermediary metabolism, particularly of the arachidonic acid cycle. Platelet abnormalities of diabetes mellitus and related changes in the endothelium probably result in an acceleration of the atherosclerotic process in these patients. Definitive experiments and followup are yet to be done to see whether or not careful control of hyperglycemia can correct some or all of these abnormalities.

Acknowledgment

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References

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