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HEMOSTATIC AND METABOLIC ABNORMALITIES IN DIABETES MELLITUS. THE SEARCH FOR A LINK

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ABSTRACT

Background. **As many as 80% of diabetic patients die from major thrombotic complications of atherosclerosis, stroke and myocardial infarction. Plasma and cellular components of the hemostatic system are often abnormal in diabetic patients, and some of these abnormalities may play a role in the high risk of thrombosis in these patients.**

Materials and Methods. **Clinical studies imply that certain hemostatic abnormalities of diabetic patients are related, to some extent, to poor metabolic control. Thus, a critical review of the data avalaible in the specialized literature has been carried out.**

Results. **Although suggestive, the link between hemostatic and metabolic abnormalities in diabetes mellitus is only circumstantial. Little is known about similarities and differences between type I and type II diabetes mellitus with respect to hemostatic parameters. Likewise, current understanding of the effects on the hemostatic system of the combination of glucose and lipid abnormalities often coexisting in diabetic patients is rather limited.**

Conclusions. ***Ad hoc*** **studies are mandatory to clarify unsolved issues in this field and define the extent to which good metabolic control is crucial to preventing the risk of thrombosis in diabetes mellitus.**

Key words: diabetes mellitus, coagulation, fibrinolysis, platelets, endothelial cells, metabolic control

It was not the purpose of this review to provide a thorough analysis of the variables playing a role in the pro-thrombotic state often present in diabetic patients (Table 1). Nor have we tried to identify subtle mechanisms leading to differences in the metabolic derangement of type I and type II diabetes. The major thrust was to review current literature on potential interrelationships between hemostatic and metabolic abnormalities in diabetes mellitus. Ischemic events such as stroke and myocardial infarction are the leading causes of morbidity and mortality both in type I and type II diabetic patients, and it would be timely to define the extent to which prevention of the metabolic derangement in diabetes mellitus is important in avoiding these thrombotic complications.

Hemostatic abnormalities in diabetes mellitus

Abnormalities of hemostatically active cells

Abnormalities of several functions of blood platelets have been reported in diabetes mellitus. The most consistent findings are related to adhesion and aggregation. Platelets from non-vasculopathic and vasculopathic type I diabetic

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Table 1. Pro-thrombotic state in diabetes mellitus.

	References
Abnormalities of platelets	Semin Hematol 1986; 33:8
Abnormalities of endothelial cells	Diab Care 1991; 14(suppl 1):160
Raised levels of coagulation factors	Hemostasis 16, 386:1986
Defects of natural anticoagulants	Hemostasis 1990; 20:263
Abnormalities of fibrinolysis	Diabetologia 1993; 36:1119

patients show an abnormally high tendency to adhere to glass.[1,2] On the other hand, these cells often exhibit increased *in vitro* aggregation in response to a variety of stimuli.[1-7] The binding of fibrinogen to specific platelet receptors is a pre-requisite for the aggregation of platelets. Parallel to increased aggregability, platelets from non-retinopathic and retinopathic type I diabetics bind abnormally high amounts of fibrinogen when exposed to thrombin, ADP or collagen.[6,7] The association between abnormally high aggregation and fibrinogen binding in diabetes is strengthened by the fact that a monoclonal antibody that inhibits the binding of fibrinogen to its platelet receptor almost corrects the abnormally high aggregability of these cells.[6,7]

Endothelial cells are known to express a series of pro-thrombotic and antithrombotic mechanisms (Table 2). Among them, prostacyclin (PGI_2) inhibits the aggregation of platelets, and tissue plasminogen activator (t-PA) triggers the degradation of fibrin by plasmin. On the other hand, the pro-coagulant (tissue-type) activity of endothelial cells (PCA) triggers a hypercoagulable state, whereas plasminogen activator inhibitor 1 (PAI-1) impairs fibrinolysis. Irrespective of the type of diabetes mellitus, most of these functions are abnormal in diabetic patients, and available data are consistent with a role for these endothelial abnormalities in the hypercoagulable state of diabetic patients.[8]

Abnormalities of coagulation and fibrinolysis

Fibrinogen is important for a series of mechanisms (e.g. platelet aggregation, blood viscosity, endothelial cell injury) thought to be important in the pathogenesis of a thrombotic event. In the '80s several epidemiological reports[9] showed an association between plasma fibrinogen levels and cardiovascular death. In those studies this association was stronger than that with serum cholesterol, and a series of factors, including high plasma glucose and glycosylated hemoglobin, were associated with abnormally high plasma fibrinogen concentrations. In some of these reports, high plasma levels of factor VII were as powerful as high plasma fibrinogen in helping predict stroke and myocardial infarction.[10,11] As for plasma fibrinogen, high factor VII levels correlated with plasma glucose.[12] Recently, infusion of glucose has been shown to cause enhancement of plasma factor VII in normals and diabetics.[13]

The coagulation cascade is a complex mechanism in which a serin protease (thrombin) leads to the conversion of a soluble protein (fibrinogen) into an insoluble one (fibrin). Thrombin is the central enzyme of the coagulation system, and a series of plasma inhibitors, defined as natural anticoagulants, prevent the

Table 2. Endothelial variables in diabetes mellitus.

parameter	*variation*	*references*
PGI2	↓	Thromb Haemostas 1988; 60:174
PCA	↑	Diabetes 1989; 38:212
t-PA	↑	Arteriosclerosis 1988; 8:68 Diabetes 1992; 41:253
PAI	↑	Thromb Haemostas 1989; 61:378
vWF	↑	Haemostasis 1986; 16:386

Legend: ↑ increased; ↓ reduced.

Table 3. Endothelial variables in diabetes mellitus.

Inhibitor	*Variation*	*References*
ATIII (functional)	↓	Thromb Haemost 1983; 50:633
ATIII (antigen)	=	Diabetes 1987; 36:320
HC II	↓	Haemostas 1990; 20:357
α2 macroglobulin	↑	Lancet 1976; 1:779
Protein C	↓	Diabetes 1986; 35:617
Plasma thrombomodulin	↑	Diabetes 1990; 39:983 Clin Chem 1991; 37:269
Protein S	↓	Diabetes 1990; 39:447

Legend: ↑ increased; ↓ reduced: = normal.

triggering of a hypercoagulable state.[14] Studies in patients with abnormalities of these inhibitors indicate that low levels of them reflect a hypercoagulable state and a severe tendency to thrombosis.[14] Among the natural anticoagulants, thrombomodulin binds thrombin in the circulation as well as on the surface of endothelial cells; the two plasma antithrombins, anti-thrombin III (ATIII) and heparin cofactor II (HCII), form one-to-one complexes with thrombin, and protein C and protein S prevent the *de novo* formation of thrombin molecules. Reduced plasma levels of natural anticoagulants have been reported in both type I and type II diabetic patients (Table 3), and an inverse correlation between good metabolic control and abnormalities of these coagulation inhibitors has been reported.[15,16] However, the latter concepts have been disputed.[17-19]

A series of activators and inhibitors of the fibrinolytic process are abnormal in diabetes mellitus (Table 4). Type II diabetic patients especially have increased levels of t-PA and its inhibitor PAI-1. However, the enhancement of plasma PAI in these patients is higher than that of t-PA. Therefore a hypofibrinolytic state occurs in diabetes. This situation is often present in patients prone to thrombotic events.[20] Abnormally high levels of another inhibitor of fibrinolysis, Lp(a), have been reported in diabetic patients and may contribute to their thrombotic tendency.[21] However, conflicting data (Table 4) are available on this issue.

The search for a link

Non-enzymatic glycosylation (glycation), oxidative stress and defective vascular synthesis of glycosaminoglycans (GAGs) are thought to play a major role in the hemostatic abnormalities of diabetic subjects. Glycation occurs in hyperglycemic states[22] and is characterized by the reversible interaction of a glucose molecule with an amino free terminus of a protein (Schiff's base). This is followed by the irreversible conversion of the product into a ketoamine via Amadori's reaction. Further interaction with other sugars and amino groups leads to the formation of advanced glycosylation end products. If the glycated site is important for major protein functions, the non-enzymatic event causes major dysfunctions (Table 5). For instance, this may impair platelet membrane fluidity and enhance sensitivity to thrombin.[23] When incubated in the presence of concentrations of glucose comparable to those found in some partially compensated type II diabetic patients, glycation has been demonstrated to affect the *in vitro* function of ATIII. This inhibitory effect depends on the interac-

Table 4. Endothelial variables in diabetes mellitus.

inhibitor	*variation*	*references*
t-PA	↑	Atherosclerosis 1988; 8:68 Thromb Haemostas 1989; 61:370
PAI-1°	↑	Diabetologia 1991; 34:457
PAI-1*	↑=	Thromb Haemostas 1992; 58:400
Lp(a)	↑=	Ann Int Med 1992; 117:42 Diabetes 1992; 41:1267

Legend: ↑ increased; = normal;°diabetes mellitus; *hyperinsulinemic state.

Table 5. Non-enzymatic glycation and hemostatic implications.

Antithrombin III	Diabetes 1988; 37:1103
Heparin cofactor II	Diabetologia 1990; 33:205
Fibrin	Diabetes 1983; 32:600
Plasminogen	Enzyme 1988, 40:140
Platelet membrane fluidity	Thromb Haemostas 1992; 65:567
PCA generation by HUVEC	J Exp Med 1989; 170:1387
Synthesis of GAG by HUVEC	J Biol Chem 1983; 258:11672

tion of glucose with the heparin binding site. Therefore heparin prevents the abnormalities of ATIII induced by hyperglycemia.[24,25] A dysfunction comparable to that described for ATIII has been reported for HCII, a natural anticoagulant that is actively glycated *in vitro*.[26] Glycosylated plasminogen is less sensitive to profibrinolytic enzymes,[27,28] and *in vitro* glycation renders fibrin rather resistant to degradation by plasmin.[29] These latter two effects may play a role in the impaired fibrinolysis of diabetics.

Autoxidation of glucose is a common consequence of high plasma levels of this sugar. This oxidative event and the release of free radicals from glycated proteins are thought to cause oxidative stress,[30] a phenomenon often suspected in patients with diabetes mellitus. This may cause major effects on the hemostatic system (Table 6). Heparan-sulphate is a negatively charged GAG synthesized by endothelial cells. The interaction of this GAG with ATIII exerts major anticoagulant effects *in vivo*.[31,32] In hyperglycemic states endothelial synthesis of GAGs is impaired,[33] and this is probably related to the effect of free radicals on the endothelium.[33] Oxidative stress may also lead to peroxidation of platelet membranes, an event that is important for the formation of prostaglandins and thromboxane. These arachidonic acid metabolites are likely to play a role in the thrombotic tendency of diabetic patients. Drugs such as aspirin are able to suppress the formation of these arachidonic acid metabolites and thus lower, to some extent, the occurrence of ischemic events in these patients.[34,35] In type II diabetes mellitus, Davì et al.[36] demonstrated that diabetic patients for whom insulin sufficed to normalize serum fructosamine levels showed corrected platelet aggregation and urinary excretion of a platelet thromboxane metabolite. In contrast, subjects in whom fructosamine was elevated showed abnormally high platelet aggregation and excretion of the metabolite.

Pharmacological evidence

A series of pharmacological data further support the possibility of a link between glycation, glucose autoxidation and hemostatic abnormalities in diabetes. Fibrates have been reported to be beneficial in diabetics.[37-39] In addition to their fibrinogen-lowering effect, these drugs have an antioxidant potential that may counteract the effects of glucose autoxidation. In keeping with this, the glucose-lowering effect of the sulphonylureas is associated with impaired synthesis of prostaglandins and thromboxane in platelets from type II diabetic patients.[40] Likewise, the antioxidant vit. E affects prostaglandin and thromboxane synthesis in platelets and endothelial cells from diabetics.[41] Other data also support an association between metabolic and hemostatic abnormalities in diabetes mellitus. A fibrate derivative, gemfibrozil, reduces the

Table 6. Glucose autoxidation and oxidative stress.

Impaired activation of ATIII	Diabetes 1987; 36:320
Platelet membrane peroxidation	Diabetes 1982; 31:947
Endothelial cell injury	Diabetes 1992; 35suppl:397
Activation of the coagulation system	Agents Actions 1987; 22:347

levels of PAI-1[42] and prothrombin fragment F1+2[43] in patients with coronary heart disease. The sulphonylurea compound glipizide stimulates fibrinolysis in cultured endothelial cells.[44] The mixture of a rapid-migration heparin and dermatan sulfate sulodexide reduces the tendency to thrombosis in humans[45] and corrects, at least in part, the pro-thrombotic state of type I diabetic patients.[46]

Conclusions

Although suggestive, the data available so far are rather circumstantial and do not clarify the extent to which metabolic abnormalities affect the hemostatic system in diabetes mellitus. In a recent ten-year study on cardiovascular mortality in type II diabetic patients,[34] it was stressed that, in addition to a lack of information about how tight the glycemic control was, the inconclusive results regarding a potential relationship between hemostatic and metabolic abnormalities in diabetes mellitus are probably related to the limited knowledge concerning similarities and differences between type I and type II diabetes mellitus with respect to hemostatic parameters. Likewise, little is known about the effects on the hemostatic system of the combination of glucose and lipid abnormalities that often coexist in diabetic patients.[47] On the other hand, major issues outlined in the preceding paragraphs still need to be addressed.

Experimental evidence indicates that following incubation with glucose, purified fibrinogen becomes resistant to plasmin-induced lysis.[29] However, in our experience, the presence of heavily glycosylated fibrinogen in diabetic patients is rather uncommon. On the other hand, there is little current evidence that increased synthesis of prostaglandins and thromboxane is the only mechanism involved in the increased aggregation and binding of fibrinogen to platelets from certain diabetic patients. We have reported that in platelets from retinopathic subjects suppression of thromboxane synthesis and scavenging of nucleotides does not suppress platelet fibrinogen binding and aggregation.[7] In keeping with this, aspirin exhibited only a limited beneficial effect in preventing ischemic events in diabetic patients.[34,35] This raises the issue as to whether aspirin is the only anti-platelet drug to employ in these patients.

These examples imply that much work is needed to address the issue of the interrelationship between poor metabolic control and the tendency to thrombosis in diabetes mellitus. In addition to the issues raised by Uusituba et al.,[47] we believe that prospective studies in selected type I and type II patients, aimed at elucidating the timing and the effects of poor metabolic control on selected hemostatic parameters, on Na^+/K^+ countertransport (an important mechanism in the regulation of blood pressure and of major functions of hemostatically active cells such as platelets and monocytes), on the vasodilating potential of the vessel wall (e.g. EDRF) and on the urinary excretion of vascular PgI_2 metabolites may help provide some insights. Besides its obvious pathophysiological significance, new information from these studies will be important for definying new, comprehensive strategies against the commonest cause of death in diabetic patients.

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