Platelet Function During Continuous Insulin Infusion Treatment in Insulin-dependent Diabetic Patients

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SUMMARY
Patients with diabetes mellitus manifest increased in vitro platelet aggregation and increased synthesis of the proaggregant and vasoconstrictor, thromboxane A₂ (TXA₂). We studied the effects of continuous insulin infusion treatment on platelet aggregation and arachidonic acid (AA)-stimulated platelet TXA₂ synthesis (15 and 30 s post-AA, 1 mM) in 16 type 1 diabetic patients. Strict glycemic control was induced with the Biostator for 2 days and maintained for 12-14 days with continuous subcutaneous insulin infusion (CSII). The average premeal plasma glucose level (4/day) fell from 184 ± 15, before treatment, to 107 ± 6 mg/dl on the final day (P < 0.001). After control, platelet synthesis of TXA₂, measured by radioimmunoassay of its stable metabolite, immunoreactive TXB₂ (iTXB₂), decreased in all patients (30 s: 276 ± 31 versus 199 ± 28 ng iTXB₂/ml/5 x 10⁹ platelets; P < 0.05). The reduction in platelet iTXB₂ synthesis (15 and 30 s) was greater in poorly controlled patients (HbA₁c >12%; N = 8), and for all patients the decrease in iTXB₂ (15 and 30 s) was correlated with the prestudy HbA₁c level (15 s: r = 0.6; P < 0.01).

In contrast, platelet aggregation responses did not improve during intensive insulin treatment. The ED₅₀ for AA (dose producing 50% maximum aggregation at 1 min) was unchanged after 2 wk of treatment and the ED₅₀ for aggregation induced by ADP fell significantly in patients with HbA₁c >12% (2.8 ± 1.3 versus 1.2 ± 0.6 μM; P < 0.01). Other factors that were associated in this study with platelet aggregation responses were plasma lipoprotein levels and microvascular disease. In all patients before treatment, the ED₅₀ for AA was inversely correlated with the LDL-cholesterol level (r = 0.57; P < 0.01). Although platelet aggregation did not improve during the period of intensive treatment, when the relations of microvascular disease and glycemic control to platelet aggregation were analyzed together in all patients, the ED₅₀ for AA was greatest (P < 0.02) in those patients without microvascular disease and HbA₁c <12%, indicating less platelet aggregability.

Thus, a brief period of CSII treatment reduced AA-stimulated platelet iTXB₂ generation; however, the effects of this treatment on platelet aggregation appear to be complex and other extraplatelet factors also seem to influence the aggregation response. DIABETES 1985; 34:1127-33.

It is well established that patients with diabetes mellitus show an increased rate of vascular complications. Microvascular disease of the kidney and eye, as well as accelerated atherosclerosis of major vessels, are apparent in both insulin-dependent (IDDM) and non-insulin-dependent diabetic patients (NIDDM). Although the difference with which these two angio-pathies predominate in type I and type II patients suggests some apparent differences in pathophysiologic factors, a role of enhanced platelet aggregation has been suggested in the pathogenesis of both microvascular and macrovascular disease.

Platelets from patients with diabetes mellitus show increased in vitro aggregability in response to a variety of agents. It has previously been reported that platelets from insulin-requiring diabetic patients produce greater quantities of the proaggregant thromboxane A₂ (TXA₂), compared with normal subjects, and that this may contribute to enhanced platelet aggregation. This notion is supported in part by the finding that platelet aggregation response to arachidonic acid in those patients was inhibited less by 13-azaprostanoic acid, an antagonist of TXA₂ action. In the same study, the arachidonic acid-stimulated TXA₂ synthesis rate was correlated with the fasting plasma glucose level measured when platelet function was studied, suggesting that platelet dys-
function in diabetes might be related to the disordered metabolic state and might be corrected by more intensive insulin treatment.

The purpose of the present study was to prospectively determine the effects of CSII treatment on platelet aggregation and platelet TXA₂ production (measured as the stable metabolite, iTXB₂) in patients with IDDM. Vascular disease and plasma lipoproteins, factors known to influence platelet function, were also assessed in this study to gain additional insight about the effects and interactions of these factors on platelet function.

MATERIALS AND METHODS

Patients. Seven male and nine female IDDM patients were studied in the General Clinical Research Center of the Medical University of South Carolina Hospital. All patients were within 15% of ideal weight, according to standard height/weight tables, and were ketosis-prone by history. Their average age was 22 ± 2.3 yr (mean ± SEM) and ranged from 13 to 52 yr. The duration of diabetes was 11 ± 4 yr and ranged from 4 to 24 yr. Retinal color fundus photographs and fluorescein angiography showed retinopathy in eight patients. Four of these had background changes, two had advanced background retinopathy considered to be preprolif-erative, and two patients had received laser photoocoagulation for proliferative retinopathy. The latter two patients also had clinical nephropathy (urinary protein >0.5 g/24 h). Before study, all patients were being treated with one or two daily injections of insulin. Their doses of intermediate-acting (NPH or lente) and regular insulin averaged 40 ± 4.7 U/day and 9.4 ± 1.7 U/day, respectively.

Protocol. The study protocol was approved by the Institutional Review Board for Human Research and informed consent was obtained from all patients or guardians before study. Patients were admitted to the hospital and fasted overnight for 12 h. Before receiving insulin, blood was collected for measurement of in vitro platelet aggregation, platelet thromboxane synthesis, and plasma lipoprotein levels. Platelet and lipoprotein studies were repeated after 12–14 days of intensive insulin treatment.

Intensive treatment was carried out using both closed-loop and open-loop continuous insulin delivery systems. Patients were first treated for 36–48 h with the Biostator Glucose Controller (Life Science Instruments, Miles Laboratories, Elkhart, Indiana) to obtain near-normal excursion of plasma glucose. Algorithms for insulin and glucose delivery were programmed as previously described. After this period of treatment with the Biostator, ambulation was encouraged and patients were instructed to walk at least 30 min after each meal.

Platelet studies. Blood for platelet studies was collected by free flow through a 19-gauge butterfly needle into a siliconized cylinder containing 3.8% sodium citrate (1:9). Platelet-rich and platelet-poor plasma were prepared according to described methods. Platelet aggregation was measured in a Model 300 Chronolog Aggregometer by the method of Born. Percent aggregation was determined assuming that a platelet-poor plasma blank represented 100% aggregation and platelet-rich plasma represented 0% aggregation. Aggregation responses to arachidonic acid (0.1–0.8 mM) and adenosine diphosphate (ADP, 0.01–10 μM) were measured. The ED₅₀ for each aggregating agent was calculated as the dose producing 50% of maximum aggregation at 1 min after addition of the agent.

Platelet thromboxane A₂ (TXA₂) synthesis was measured as previously described. Exactly 15 and 30 s after addition of arachidonic acid to the aggregometer (final concentration of 1 mM), 50-μl aliquots were withdrawn from the platelet-rich plasma and placed in 0.95 ml imidazole solution (500 μg/ml in thromboxane assay buffer) at 4°C, then immediately frozen to stop thromboxane generation. Immunoreactive thromboxane B₂ (iTXB₂), the stable metabolite of TXA₂, was measured directly in aliquots of this solution (0.01–0.02 ml) using a previously described radioimmunoassay. Synthesis of TXA₂ at 15 and 30 s was expressed as ng iTXB₂/ml/5 × 10⁵ platelets.

Plasma lipoproteins. Blood for lipid and lipoprotein assays was collected in EDTA (1 mg/ml of blood) and the plasma separated and immediately refrigerated. The separation of lipoproteins was performed by ultracentrifugation as previously described. After ultracentrifugation, very-low-density lipoprotein (VLDL) was removed from the top layer, and the high-density lipoprotein (HDL) plus low-density lipoprotein (LDL) cholesterol level was measured in the infranatant. HDL cholesterol was separately measured in the supernatant obtained after precipitation of LDL and VLDL from whole plasma with phosphotungstate and MgCl₂ as previously described. The LDL-cholesterol level was derived by subtracting the HDL-cholesterol level from the HDL-plus-LDL-cholesterol level. Cholesterol and triglyceride levels were measured using the semiautomated method standardized by the Lipid Research Clinics Program.

Other assays. Blood glucose levels were measured on capillary blood with a reflectance meter (Dextrometer, Ames Co., Miles Laboratories), the accuracy of which was verified daily by an autoanalyzer glucose-oxidase method. Urine glucose was measured by the glucose-oxidase method and excretion was expressed as grams per twenty-four hours. Hemoglobin A₁c (HbA₁c) was measured in erythrocyte hemolysates of fasting blood samples by isoelectric focusing over a pH gradient of 6–8, according to the method of Spicer et al. This method does not measure the labile component of glycosylated hemoglobin. Normal levels with this method range from 4% to 6.7%.

Materials. The following were purchased from commercial sources: [³H]-TXB₂, 150 Ci/mmol (New England Nuclear, Boston, Massachusetts); adenosine diphosphate (Sigma...
of initial platelet studies. Patients with a HbA1c level >12% were considered to be in good-to-fair control.

Results of treatment on plasma and urinary glucose and plasma lipoprotein levels. The effects of 2 wk of CSII treatment on plasma and urinary glucose and plasma lipoproteins are shown in Table 1. On the final day of treatment, when platelet studies were repeated, premeal blood glucose levels, urinary glucose excretion, and HbA1c levels were significantly reduced compared with pretreatment levels. Although total and LDL-cholesterol and plasma triglyceride levels showed downward trends during this period, the changes were not significant for the group. The average HDL-cholesterol level also did not change significantly.

Platelet TXB2 synthesis. The effect of insulin infusion treatment on arachidonic acid-induced platelet TXB2 synthesis is shown in Figure 1. After 2 wk of CSII, there was a significant reduction in platelet TXB2 release (30 s: 276 ± 31 versus 199 ± 28 ng iTXB2/ml/5 x 10^5 platelets, P < 0.05). To further assess changes in platelet TXB2 synthesis during intensive insulin treatment, the results were analyzed according to the patient’s glycemic control before study. Prior glycemic control was assessed by the HbA1c level measured on the day of initial platelet studies. Patients with a HbA1c level >12% were considered to be in poor glycemic control and those with a level <12% considered to be in good-to-fair control. This HbA1c level was chosen because a similar level in previous studies revealed that patients categorized in this way show differences in insulin sensitivity and lipoprotein and renal metabolism. In this study, eight patients had pretreatment HbA1c levels >12% and eight patients had levels <12% (Figure 1). In the subgroup of patients with pretreatment HbA1c >12%, platelet TXB2 synthesis fell significantly during insulin infusion treatment (30 s: 321 ± 52 versus 196 ± 46 ng iTXB2/ml/5 x 10^5 platelets, P < 0.05). However, in those with initial HbA1c <12%, there was no significant change in iTXB2 synthesis during the same period (233 ± 32 versus 202 ± 43 ng iTXB2/ml/5 x 10^5 platelets, P = NS). This relationship between initial HbA1c level and subsequent change in platelet TXB2 synthesis during treatment was also noted in the iTXB2 levels measured at 15 s after initiation of aggregation. Only patients with pretreatment HbA1c >12% showed a significant reduction in iTXB2 synthesis at 15 s of aggregation (164 ± 34 versus 98 ± 33 ng iTXB2/ml/5 x 10^5 platelets, P < 0.05). Neither the patients with HbA1c <12% nor the group of patients as a whole showed significant changes in iTXB2 at 15 s (109 ± 16 versus 105 ± 21 and 136 ± 20 versus 102 ± 15 ng iTXB2/ml/5 x 10^5 platelets, respectively; P = NS for both). Furthermore, in all patients, the change in platelet-generated iTXB2 (15 s) after 2 wk of treatment was correlated with the pretreatment HbA1c level (r = 0.6, P < 0.01; ΔiTXB2 = 184 – 19 x HbA1c%, Figure 2). A similar significant correlation existed between the HbA1c level and change in iTXB2 production measured at 30 s. Thus, patients with the greatest degree of hyperglycemia before treatment demonstrated the greatest reduction in arachidonic acid-induced platelet TXB2 synthesis after a period of intensive insulin treatment aimed at normalizing glycemic excursion.

Platelet aggregation. The ED50 (dose producing 50% aggregation at 1 min) was determined for arachidonic acid- and ADP-induced aggregation before and after intensive insulin treatment. When aggregation data for the entire group of patients were analyzed, no changes in the ED50 for arachidonic acid or ADP occurred after treatment. Table 2 shows pre- and posttreatment ED50 levels for arachidonic acid and ADP in the subgroups of patients divided according to pre-
Platelet Function During CSII in IDDM Patients

Treatment HbA₁c levels. Arachidonic acid-induced aggregation was unchanged after treatment in either subgroup. In contrast to the results with arachidonic acid, in patients with HbA₁c >12% the ED₅₀ for ADP fell significantly after CSII treatment. Therefore, in these patients platelets appeared to become more sensitive to aggregation induced by ADP.

Although intensive insulin treatment did not change the ED₅₀ for arachidonic acid-induced platelet aggregation, relations found between this value and plasma lipoprotein levels, both before and after treatment, suggest that plasma lipoproteins may influence platelet function. Before treatment, the ED₅₀ values for arachidonic acid in all patients were inversely correlated with their low-density-lipoprotein (LDL) cholesterol levels (r = 0.57, P < 0.01; ED₅₀ = 0.71 - 0.003 × LDL-cholesterol [mg/dl]). Furthermore, after 2 wk of CSII, the percent change in the ED₅₀ for arachidonic acid was directly correlated with the change in high density lipoprotein (HDL) cholesterol level (r = 0.6, P < 0.01; % ΔED₅₀ = 15.3 + 2.6 × ΔHDL-cholesterol [mg/dl]).

Relationship of vascular disease to platelet function. Because it has been suggested that vascular disease alters platelet function, we analyzed our results to determine whether there was any relationship between vascular disease and platelet function, or between vascular disease and platelet function in patients categorized by HbA₁c as being in poor or good-to-fair glycemic control before study. According to retinal studies, there were eight patients with and eight without microvascular disease. Patients within these groups were distributed between those with initial HbA₁c >12% and HbA₁c <12%, such that an analysis of possible interaction between vascular disease and control could be performed (Table 3). Data from both pre- and posttreatment studies were used in this analysis.

Microvascular disease alone was not associated with differences in platelet aggregation or thromboxane synthesis in our study. However, analyzing platelet aggregation in relationship to both microvascular disease and glycemic control showed that, in patients without detectable microvascular disease, a greater difference in arachidonic acid ED₅₀ was found between the groups with HbA₁c <12% and >12% than in patients with microvascular disease (Table 3). That is, in patients without microvascular disease, whose HbA₁c level showed good-to-fair prior glycemic control (HbA₁c <12%), platelet aggregation response to arachidonic acid was less than in patients in poor control (HbA₁c >12%). This difference related to glycemic control was not apparent in patients with microvascular disease. No association between glycemic control and arachidonic acid-induced aggregation was observed when vascular disease was not taken into account (Table 2). No association between microvascular disease and platelet aggregation response to ADP was found, either for vascular disease independently, or when vascular disease was related to glycemic control. However, the increased sensitivity of platelets to ADP after 2 wk of treatment, which occurred in patients with initial HbA₁c >12%, was confirmed in this analysis. This change in ADP-induced aggregation after treatment was independent of the presence or absence of microvascular disease.

Platelet ITXB₂ synthesis was also analyzed in patients with or without microvascular disease. Although it did not reach
to platelet aggregation besides TXA2, which were not as-
This possibility is supported by the finding that dose-re-
though iTXB2 levels fell substantially in some patients after
sponse curves for inhibition of arachidonic acid-induced
aggregation response to ADP increased in those patients showing the greatest re-
ments could be a direct result of changes in plasma glucose
of fibrinogen or other platelet-active proteins after treatment
could have influenced either arachidonic acid- or ADP-in-
duced aggregation.22–24
Changes in platelet function during intensive insulin treat-
ment could be a direct result of changes in plasma glucose
or insulin levels, or could be secondary to changes in other
metabolites or hormones. Direct effects of glucose and insulin
on platelets have been studied. High glucose concentrations
in vitro were found to suppress aggregation induced by ar-
achidonic acid,6 but have no effect on arachidonic acid-in-
duced aggregation.25 Increasing the glucose concentrations in
pharmacologic concentration in the plasma insulin level has been reported to directly inhibit
ADP-induced aggregation, and this effect was synergistic
with the effect of raised glucose concentration.26 Also, after
intravenous infusion of insulin in diabetic patients, the ag-
ggregation response to ADP was found to be suppressed.28
Although plasma glucose levels were lowered and plasma
insulin levels may have been changed as a result of CSII
treatment in our study, it is difficult to attribute all of the
changes we observed in platelet function to changes in
plasma glucose or insulin.

Plasma lipoproteins and vascular disease may have influ-
enced arachidonic acid-induced platelet aggregation. Be-
fore treatment, the ED50 for arachidonic acid was inversely
correlated with the plasma level of LDL-cholesterol, and after
treatment the change in arachidonic acid ED50 correlated
directly with the change in plasma HDL-cholesterol. An in-
fluence of plasma cholesterol levels on platelet function has
been suggested in several previous studies. Platelets from
patients with type II hypercholesterolemia show increased
sensitivity to aggregating agents.29 Shattil et al.30 showed that

**TABLE 3**
Relationship of vascular disease and glycemic control to platelet function in IDDM patients*

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*Values in this table were derived using data from both pretreatment and posttreatment platelet studies. HbA1c levels are pretreatment values. The statistical analysis derives a common error term and therefore individual standard error values are not given. See Table 2 for definition of ED50.

†In patients without microvascular disease, the difference in ED50 values between this group and the group with HbA1c >12% is greater (P < 0.02) than the difference between comparable groups with microvascular disease (cf. columns 1 and 2).

‡P = 0.08 compared with all other groups.

a statistically significant level (P = 0.08), patients without mi-
crovascular disease and lower HbA1c levels tended to have
the lowest level of platelet iTXB2 synthesis (Table 3).

**DISCUSSION**

During a period of 2 wk of CSII treatment, arachidonic acid-
induced platelet thromboxane synthesis was reduced in this
group of IDDM patients. This reduction was greatest in pa-
patients who were in poor glycemic control before study, as
defined by HbA1c >12%. Surprisingly, during the same pe-
period, platelet aggregation response to arachidonic acid did
not change, as measured by the ED50 for arachidonic acid.
In contrast, the ED50 for ADP increased in patients with
HbA1c >12%, demonstrating increased aggregability in re-
sponse to ADP.

The fall in arachidonic acid-induced platelet iTXB2 synthe-
sis after glycemic control is consistent with the association
found previously between plasma glucose levels and TXB2
production.6 McDonald et al.,17 in a cross-sectional study,
also found that platelets from IDDM patients being treated
with insulin infusion pumps produced less TXB2 in response
to arachidonic acid or collagen than did platelets from pa-
tients on conventional insulin therapy.

In view of the decreased iTXB2 production during intensive
insulin treatment in these studies, it is interesting that we did
not find a change in the aggregation response to arachidonic
acid. Since aggregation represents the summation of effects
of several interrelated mechanisms, and platelet sensitivity
to ADP increased in those patients showing the greatest re-
duction in thromboxane production, perhaps these changes
represent offsetting effects on aggregation. Platelet aggrega-
tion response to arachidonic acid, measured at 1 min, may
require only a threshold level of TXA2 production, and al-
though iTXB2 levels fell substantially in some patients after
treatment (Figure 1), measurable levels were still observed.
This possibility is supported by the finding that dose-re-
ponse curves for inhibition of arachidonic acid-induced
platelet aggregation, and iTXB2 production, by a thrombox-
an synthase inhibitor are not superimposable.18 Synthesis
of iTXB2 can be inhibited by >90% without inhibition of the
aggregation response.

Arachidonic acid can also activate other pathways leading
to platelet aggregation besides TXA2, which were not as-
essed in this study. Prostaglandin H2 can aggregate plate-
lets,30 and not all of its products, nor the sum total of its
metabolites, were measured in this study. Arachidonic acid,
like ADP, exposes platelet fibrinogen-binding sites and a role
for fibrinogen in platelet aggregation is generally ac-
cepted.2021 Since our studies were done in platelet-rich
plasma, where exposure to fibrinogen could occur after the
addition of these aggregating agents, a change in the levels
of fibrinogen or other platelet-active proteins after treatment
could have influenced either arachidonic acid- or ADP-in-
duced aggregation.22–24

Plasma lipoproteins and vascular disease may have influ-
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‡P = 0.08 compared with all other groups.
incubation of platelets with cholesterol-rich liposomes, which increased platelet membrane cholesterol, resulted in increased platelet sensitivity to epinephrine- and ADP-induced aggregation. Platelet arachidonic acid metabolism and TXB₂ production are also augmented after an increase in platelet cholesterol content. These findings may be relevant to our observation that the arachidonic acid ED₅₀ was negatively correlated with plasma LDL-cholesterol levels. The relation we found between HDL-cholesterol and arachidonic acid-induced aggregation is also consistent with reports that isolated HDL reduces platelet aggregation and release response. Taken together, these observations suggest that plasma lipoproteins may have influenced platelet aggregation in the present study.

In our study, vascular disease may also have had some influence on the responses of platelet function to metabolic control. The presence of microvascular disease by itself was not associated with significant alterations in platelet function; however, in patients without microangiopathy, a greater difference in arachidonic acid ED₅₀ was attributable to the HbA₁c level than in patients with microangiopathy (Table 3). These findings suggest that beneficial effects of metabolic control on platelet function occur in the absence of vascular disease, but after the development of vascular disease, control may have less impact. This was also apparent from the trend toward lower iTXB₂ synthesis in patients without microvascular disease and with HbA₁c <12% (Table 3). Butkus et al.³² have reported that microvascular disease is associated with significantly greater arachidonic acid-induced platelet TXB₂ release in IDDM patients. Although consistent with previous notions, the influence of vascular disease on platelet function suggested by our data are based on analysis of small numbers of patients and await confirmation by a study of a larger series of patients.

Understanding the influence of preexisting vascular disease on subsequent effects of intensive insulin treatment is now of particular importance in view of recent studies suggesting that the course of retinopathy may accelerate after treatment aimed at strict glycemic control, particularly in patients with existing vascular disease.²⁴²⁵ One preliminary report suggests that acceleration of retinopathy after instituting tight glucose control occurs more frequently in patients that have been poorly controlled.²⁶ Our finding that the platelet aggregation response to ADP was significantly increased after insulin infusion treatment in patients with HbA₁c >12%, as well as the relationship of vascular disease to the effects of metabolic control on platelet function, raises questions about the role of platelets in the deterioration of retinopathy observed in some patients treated intensively. If enhanced platelet aggregation was contributing to this process, concurrent treatment with antiplatelet agents might be helpful.

In summary, the present study shows that the effects of CSII treatment on platelet aggregation in IDDM patients are complex; however, control reduces platelet TXA₂ synthesis, which could be viewed as a beneficial effect in relation to the progression of vascular disease.

ACKNOWLEDGMENTS
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