Fibrinolytic activity in type II diabetes mellitus and the effect of glycemic control on fibrinolytic parameters

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Fibrinolytic parameters including tissue-type plasminogen activator (t-PA) antigen and plasminogen activator inhibitor-1 (PAI-1) antigen were studied in 34 poorly controlled type 2 diabetic patients. Age and sex matched 23 healthy subjects with normal glucose concentration comprised the control group. The diabetic patients had a significantly higher mean PAI-1 and t-PA antigen levels compared to control group (p<0.05), but elevation of PAI-1 was higher than t-PA antigen resulting decrement in fibrinolytic capacity. t-PA and PAI-1 was significantly correlated with body mass index (p<0.05), but not with age, triglyceride, cholesterol, HDL, LDL, and HbA1C. To determine the effect of improved glycemic control on fibrinolytic activity, we measured changes in plasma t-PA and PAI after 3 months treatment with insulin (14 patients) or gliclazide (14 patients). Although there was a trend to falling in PAI-1 and increasing in t-PA resulting in a slight improvement of the fibrinolytic impairment, these changes were not statistically significant.

Key Words: Diabetes mellitus, Fibrinolytic activity, Plasminogen activator inhibitor

Atherosclerosis and atherosclerosis-related complications represent the primary cause of morbidity and premature mortality in patients with diabetes mellitus (1-3). Changes in coagulation, fibrinolysis, platelet and vessel wall function are accepted to contribute to micro and macroangiopathy (4,5). Fibrin deposit could play a role in the development of atherosclerotic lesions possibly an initiating factor of endothelial cell injury. Since it leads to the decreased removal of fibrin deposit, hypofibrinolysis would be a prime candidate for a role in the initiation and development of atherothrombosis (6,7).

Studies of the fibrinolytic system in patients with diabetes have yielded contradictory results. Fibrinolytic activity in basal conditions was reported to be decreased (8-11), normal (12), or increased (13,14). In view of these discrepancies in data reported by various laboratories, we decided to examine fibrinolytic parameters in patients with type 2 diabetes mellitus and to prospectively determine the effects of improved glycemic control on fibrinolytic parameters.

MATERIALS AND METHODS

Thirtyfour type 2 diabetic patients, consisting of 17 males and 17 females were included in the study. The known duration of the disease ranged from 1 to 25 years. Before this study, 13 patients were being treated with insulin and 21 patients with diet and oral hypoglycemic drugs. But they were in poor glycemic control because of many reasons. During this study, patients separated into two treatment groups. 14 patients were treated with insulin, and 20 patients with gliclazide. They were controlled at weekly intervals and adjustments in insulin and gliclazide dosages were made as needed. 6 patients who were in the gliclazide group were excluded from the study because of inadequate controls.

A group of 23 healthy volunteers, matched for age and sex, with normal glucose concentration and no family history of diabetes and no clinical or electrocardiographic evidence of ischemic heart disease or hypertension comprised the control group.

Blood from an antecubital vein for estimation of fibrinolytic parameters was collected from resting patients or controls between 8.00 and 9.00 a.m. after a 12 hours fast into plastic tubes containing sodium citrate (nine parts of blood were mixed with one part of 3.8% sodium citrate) and centrifuged for 15 minutes at 3000 g and the plasma was then stored at -70°C.
until analyzed. All samples were assayed in one session in order to reduce inter assay variations.

Fibrinolytic parameters including plasminogen activator inhibitor antigen (PAI-1) and tissue plasminogen activator (t-PA) were measured by enzyme linked immunosorbent assay (ELISA) using commercial test kits (Asserachrom t-PA and asserachrom PAI-1, Diagnostica Stago, France).

Serum parameters such as albumin, creatinine, glucose, cholesterol, triglyceride, LDL and HDL cholesterol and HbA1C were measured using standard procedures.

All of the parameters were repeated after three months of therapy in diabetic patients. Pre treatment and post treatment values were compared.

**Statistical analysis:** Correlations were determined by linear regression analysis. Comparison were performed using the Student’s t test (between patients and control groups) Mann-Whitney test (between subgroups of patients) and Wilcoxon matched-pairs signed rank test (between pre-treatment and post-treatment values).

**RESULTS**

Table 1 shows the means and standard errors of various parameters in diabetic and control subjects. There were no differences in age, sex, total cholesterol, blood pressure, and LDL cholesterol between the two groups. As expected, diabetic subjects had significantly higher body mass index (BMI), higher fasting plasma glucose and triglyceride levels and lower HDL cholesterol levels than control group.

The mean concentration of PAI-1 antigen was significantly higher in the diabetic subjects compared with the control subjects (26 ng/ml vs 9.4 ng/ml). t-PA and PAI were further analyzed with respect to presence of retinopathy. Fourteen patients had retinopathy. There were no significant differences between the two groups. t-PA and PAI were further analyzed with respect to presence of retinopathy. Fourteen patients had retinopathy. There were no significant differences between the two groups.

**Table 1. Parameters in diabetic subjects and normal control groups (mean standard error)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Diabetic patients</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52±2.0</td>
<td>46±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>17/17</td>
<td>12/11</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.4±0.9</td>
<td>23.9±0.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>140±6.1</td>
<td>135±4.2</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83±2.4</td>
<td>80±2.1</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1C</td>
<td>8.8±0.3</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>222±7.3</td>
<td>210±6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>178±18</td>
<td>130±9.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>140±8.1</td>
<td>90±6.4</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL Chol. (mg/dl)</td>
<td>131±8.7</td>
<td>120±3.7</td>
<td>NS</td>
</tr>
<tr>
<td>HDL Chol. (mg/dl)</td>
<td>43±5.4</td>
<td>54±3.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>t-PA (ng/ml)</td>
<td>11.7±0.9</td>
<td>7.8±0.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PAI-1 (ng/ml)</td>
<td>26.1±4.0</td>
<td>9.4±1.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NS: Not significant

**DISCUSSION**

In this study, fibrinolytic parameters were assessed in 34 type 2 diabetic patients with varying degrees of
metabolic control. We found that diabetic patients had significantly higher PAI-1 and t-PA antigen levels compared with nondiabetic control subjects. These results demonstrated that a reduced fibrinolytic activity is present in basal condition that agrees with some previous reports (8-11).

Endogenous fibrinolysis is modulated physiologically by two activators of plasminogen, t-PA and u-PA. PAI is considered to be a major regulating factor of fibrinolysis by inhibition of the plasminogen activators (15,16). A dynamic equilibrium exits between t-PA and PAI-1 on the luminal surface of vessels that determines net local fibrinolytic activity. An increase in expression of PAI-1, a decrease in the expression of t-PA, or both lead to decreased net fibrinolytic activity. In this study, diabetic subjects had threefold elevations of plasma concentrations of PAI-1 compared with values in control subjects. Whereas elevations of t-PA compared to normal subjects were lower than PAI-1. The elevated level of PAI-1 causes inhibition of t-PA, resulting in a decreased fibrinolytic capacity.

Fibrin deposited on injured endothelial cells is resolved by an activation of the fibrinolytic system. Therefore, a defective fibrinolysis will delay the resolution of fibrin and cause an increased formation of thrombus and scar tissue. Patients with diabetes mellitus is known to have high incidence of atherosclerosis.

Plasma fibrinolytic activity has been found to be diminished in many studies, including those of patients with hypertension (17), obesity and hypertriglyceridemia (18,19) and angina pectoris (20). This defect has been attributed to the increased plasma concentration of PAI-1 accompanying these disorders. We found a positive correlation of BMI with t-PA and PAI-1. This observation further supports documented decreased fibrinolytic activity in obesity. Elevated BMI predisposes to insulin resistance and hyperinsulinism rather than to insulin deficiency (10). More recently, Juhan-Vauge and coworkers have reported a positive correlation between plasma levels of insulin and PAI-1 in both normal and obese individuals and in patients with type 2 diabetes, and these authors consider insulin to be an important determinant for the regulation of endothelial cell related fibrinolysis (9).

The concentrations of t-PA and PAI-1 antigen seem to be independent of diabetes control. Since none of these measured parameters were correlated with the HbA1C level. To determine the effect of improved glycemic control on fibrinolytic activity we also measured changes in plasma t-PA and PAI after 3 months treatment with insulin or glarglize. Although there was a trend to falling in PAI and increasing in t-PA resulting in slight improvement of fibrinolytic system, results in our patients indicate that glycemic control alone in type 2 diabetes mellitus does not remarkably improve fibrinolytic activity.

REFERENCES


