Insulin Resistance Is Associated with Increased Circulating Level of Thrombin-Activatable Fibrinolysis Inhibitor in Type 2 Diabetic Patients

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Hypofibrinolysis is a common finding in patients with diabetes mellitus (DM) and obesity and a risk factor for the development of cardiovascular disease. Recently, a new potent inhibitor of fibrinolysis, the thrombin-activatable fibrinolysis inhibitor (TAFI) has been isolated and characterized from human plasma. The present study was undertaken to assess the activity and circulating level of TAFI and its relation to fibrinolytic function and obesity in patients with type 2 DM. Fifty-seven patients with type 2 DM (38 men, 19 women) were enrolled in this study. DM patients were categorized in age-matched obese (body mass index (BMI) ≥ 25) and nonobese (BMI < 25) groups. The plasma concentration and activity of TAFI were significantly (P < 0.05) higher in DM patients than in healthy controls. The plasma levels and activity of TAFI were significantly (P < 0.05) elevated in obese DM patients compared with nonobese DM and nonobese healthy subjects. RT-PCR demonstrated the expression of TAFI in human adipose tissue and in human endothelial cells. The plasma levels of TAFI were independently and significantly correlated with glucose intolerance (HbA1c), with obesity (BMI, visceral fat area), and with an indicator of insulin resistance (glucose infusion rate). This study showed that increased circulating level of TAFI may be an important causative factor of hypofibrinolysis in patients with type 2 diabetes, obesity and insulin resistance. (J Clin Endocrinol Metab 87: 660–665, 2002)

Patients with type 2 diabetes mellitus (DM) show enhanced activation of the blood coagulation system (1). This increased procoagulant activity is believed to contribute to the high incidence of premature atherosclerosis and increased morbidity and mortality, attributable to myocardial infarction, cardiovascular disease and peripheral vascular disease in diabetic patients (2). The development of thrombi within vessels results from the disruption of the equilibrium between the prethrombotic and antithrombotic factors that controls clotting homeostasis; this imbalance may occur due to an ongoing stimulus to thrombogenesis, a defect of the natural anticoagulant or fibrinolytic system. In diabetic patients, several studies have reported high plasma concentrations of procoagulant proteins and decreased concentrations of functionally attenuated anticoagulant factors (3). Hypofibrinolysis, a common finding in diabetes, may also be an important cause of vascular thrombosis; hypofibrinolysis alone is sufficient for extended fibrin deposition even without a preceding enhanced coagulation (4, 5). The clinical relevance of the fibrinolytic function in the pathogenesis of thrombosis in diabetes is illustrated by the significant and positive correlation of hypofibrinolysis with the presence and severity of macro- and microangiopathies (6, 7). Impaired fibrinolytic function is a risk factor for myocardial infarction in both nondiabetic and diabetic patients (8). It has been also reported that circulating levels of fibrinolytic factors may influence the survival of diabetic patients (9).

Hypofibrinolysis with hypercoagulable states frequently occurs in conditions associated with insulin resistance in diabetic patients (10, 11). Insulin resistance is a pluri-metabolic syndrome characterized by the presence of obesity, arterial hypertension, glucose intolerance, and biochemical abnormalities such as hyperinsulinemia, hypertriglyceridemia, and decreased high density lipoprotein cholesterol (11). In the present study, we focused our attention on the mechanism of hypofibrinolysis occurring in type 2 DM patients with obesity. Increase in the plasma antigen level and activity of plasminogen activator inhibitor (PAI)-1 and decreased capacity of the endothelium to secrete tissue plasminogen activator have been implicated in the mechanism of hypofibrinolysis associated with obesity (9). Recently, a new potent inhibitor of fibrinolysis, the thrombin-activatable fibrinolysis inhibitor (TAFI) or carboxypeptidase U, has been isolated and characterized from human plasma (12) TAFI is a glycoprotein synthesized by the liver that can be activated by thrombin-catalyzed proteolysis to a carboxypeptidase B-like enzyme that inhibits fibrinolysis (13). The possibility that TAFI also participates in the mechanism of hypofibrinolysis in obese diabetic patients has not been as yet appraised. The present study was undertaken to assess the circulating level of TAFI and its relation to fibrinolytic function and obesity in patients with type 2 DM.

Patients and Methods

Reagents

BSA and hippuryl-Arg were obtained from Sigma (St. Louis, MO), streptavidin-peroxidase conjugate from Amersham International (Buckinghamshire, UK), and tetramethylbenzidine peroxidase substrate was

Abbreviations: BMI, Body mass index; CT, computed tomography; DD, D-dimer; DM, diabetes mellitus; EIA, enzyme immunoassay; GIR, glucose infusion rate; PAI, plasminogen activator inhibitor; TAFI, thrombin-activatable fibrinolysis inhibitor; TAT, thrombin-antithrombin complex.
from Kirkegaard & Perry Laboratories (Bethesda, MD). The thrombin inhibitor H-D-Phe-Pro-Arg-chloromethylketone and the potato carboxypeptidase inhibitor were obtained from Calbiochem (La Jolla, CA). Human thrombin and recombinant thrombomodulin were prepared as described previously (14). Penicillin, streptomycin, T-pancreatin, vitamin solution, sodium pyruvate and nonessential amino acids were purchased from Life Technologies, Inc. (Grand Island, NY).

Subjects

This study comprised 57 patients (38 men, 19 women) with type 2 DM. DM was diagnosed according to the criteria of the World Health Organization, and based on the results of the 75 g oral glucose tolerance test. The age of the patients was 55.9 ± 11.8 yr old, ranging between 27 and 82 yr. The mean duration of diabetes was 9.0 ± 1 yr (range 1–30 yr). Subjects with clinical or laboratory signs of liver dysfunction, malignancy or a history of coagulation disorder were excluded from the study. Fundi of the patients were examined by an ophthalmologist. Informed consent was obtained from all patients before the beginning of the study. The study was approved by the Mie University's Review Board for human experiments and was carried out following the principles of the Helsinki Declaration. Data obtained in 20 (men 16, women 4) nonobese and in 10 (men 5, women 5) obese healthy subjects served as controls. The age between all DM (n = 57, 55.9 ± 11.8 yr old) and all healthy (n = 30, 49.7 ± 13.22 yr old) subjects was not significantly different.

Laboratory measurements

Blood samples were drawn before breakfast from an antecubital vein with plastic syringes and collected in polystyrene tubes containing anticoagulant. Blood was then centrifuged at 1,200 × g for 20 min at 4 °C. Plasma was then collected and stored in small aliquots at −80 °C until use. Blood sampling in each DM patient was carried out before the beginning of any therapy. All patients were being treated with diet alone with or without exercise therapy, but none of them has been previously treated with oral hypoglycemic agents. The plasma levels of thrombin-antithrombin complex (TAT) were measured by an enzyme immunoassay (EIA) using 96-well plate coated with antithuman TAT monoclonal antibody and, as second antibody, a biotin-labeled antihuman TAT monoclonal antibody. The interassay and intraassay coefficients of variability were less than 10%. The plasma levels of activated protein C protein C inhibitor complex was measured by EIA as previously described (15). The interassay and intraassay coefficients of variability were 5 and 7%, respectively. The plasma levels of D-dimer (DD, D-dimer test-F, Kokusai Shiyaku, Kobe, Japan) were measured using commercial EIA kits.

The plasma levels of TAFI were also measured using a commercially available EIA kit (TAFI-EIA, Kordia Laboratories, Leiden, The Netherlands). Briefly, sheep antihuman TAFI antibody, diluted in 0.1 M NaHCO3 buffer (pH 9.3), was coated on microwell plates by overnight incubation. After washing with the same buffer, blocking of unspecific bindings was performed for 3 h at room temperature with PBS containing 1% BSA. Washing with EIA buffer (0.05 M Tris-HCl, 0.15 M NaCl, pH 7.5, 0.1% BSA, 0.01% Tween 20) was then carried out, and 100 μL of horseradish peroxidase-conjugated sheep antihuman TAFI was added to each well and incubated for 1 h. After appropriate washing, peroxidase substrate was added to each well and absorbance was measured at 450 nm. The interassay and intraassay coefficients of variability were less than 10%. The activity of plasma TAFI was determined as previously described (15) Briefly, 30 μL of plasma was incubated in HEPES buffer (20 mM HEPES, 137 mM NaCl, 4 mM KCl, pH 7.4) containing 20 mM thrombin, 5 mM thrombomodulin, and 17 mM CaCl2 in a total volume of 60 μL for 10 min at room temperature. After inactivating thrombin activity with 150 μM H-D-Phe-Pro-Arg-chloromethylketone, 20 mM hippuryl-Arg, the substrate for activated TAFI, was added. Substrate conversion was allowed for 10 min at 37 °C. The reaction was stopped by adding 1 M HCl (20 μL), and the mixture was neutralized with an equal volume of 1 M NaOH. Then, 25 μL of 1 M sodium phosphate (pH7.4) and 30 μL of 2% cyanoacrylate chloride in 1,4-dioxane were added. Denatured protein and excess cyanoacrylate chloride were removed by centrifugation (2 min, 14,000 rpm), and 100 μL of the sample was transferred to a 96-well plate. The absorbance at 405 nm was measured using an ELISA plate reader. TAFI activity was determined in the presence or absence of the TAFI inhibitor carboxypeptidase inhibitor to distinguish between the constitutive carboxypeptidase activity and the inducible carboxypeptidase activity in plasma. During each experiment a standard curve of TAFI activity in normal plasma was determined by serial dilutions of normal plasma in HEPES buffer. It is worthy to note that the determined TAFI activity was not present in plasma, but was induced by incubation with the thrombin-thrombomodulin complex.

Fasting plasma glucose concentration was measured by the glucose oxidase method and hemoglobin A1c (HbA1c) was determined by HPLC. Serum insulin was measured using an immunometric assay kit (Dainabot Co., Tokyo, Japan). Blood pressure was determined in supine position after 5-min rest. The body mass index (BMI) was estimated by dividing the body weight in kilogram by the square of the height in meter. DM patients were categorized in age-matched obese (BMI ≥ 25) and nonobese (BMI < 25) groups according to BMI values, following the criteria of the Ministry of Health and Welfare of Japan (16). By using this cutoff value of BMI, the prevalence of diabetic complications have been shown to be significantly higher in the obese group compared with its nonobese counterpart (17). Healthy subjects were also categorized in obese (BMI ≥ 25) and nonobese (BMI < 25) groups according to BMI values. The body fat area was evaluated by a previously described method (18). The total cross-sectional area, the intra-abdominal visceral fat, and the sc fat areas were measured by abdominal computed tomography (CT) taken at the umbilical level. Any ip region having the same density as the sc fat layer was defined as a visceral fat area. Insulin sensitivity was evaluated by the euglycemic hyperinsulinemic clamp technique using the artificial pancreas (STG-22, NIKKISO, Tokyo, Japan) (19). The clamp study was performed for 120 min, and the desired level of serum insulin was fixed to 1200 pmol/liter. The mean values of insulin reached a stable level between 90 min and 120 min after starting the clamp study. The blood glucose was clamped to desired level (5.24 mmol/liter), and the mean amount of glucose administered in the last 30 min was regarded as the glucose infusion rate (GIR).

Cell culture

The human hepatic HepG2 cell line was obtained from RIKEN Cell Bank (Ibaraki, Japan) and the human umbilical vein endothelial cells (HUVECs) from Sanko Junyaku (Tokyo, Japan). HUVECs were cultured in MCDB131 medium (Chloro Research Industry, Tokyo, Japan) supplemented with 5% heat-inactivated FBS (Life Technologies, Inc., Grand Island, NY), 50 μg/ml gentamycin (Nacalai Tesque), 50 ng/ml amphotordin B (Bristol-Myers Squibb, New Brunswick, NJ), 50 μg/ml ascorbic acid, 0.5 μg/ml hydrocortisone, 10 μg/ml vascular endothelial cell growth factor (Becton Dickinson and Co., Bedford, MA), 8 ng/ml fibroblast growth factor, and 20 ng/ml epithelial growth factor. The cells were cultured in DMEM (Life Technologies, Inc.) containing 10% heat-inactivated FBS BioWhittaker, Inc. Walkersville, MD), 50 μg/ml penicillin, 50 μg/ml streptomycin, 2 mM T-glutamine, 2% vitamin solution, 110 μg/ml sodium pyruvate, and 0.1 mm nonessential amino acids. All cells were cultured in 10-cm dishes in an atmosphere composed of 5% CO2 and 95% air. Confluent cells were harvested by a brief exposure to 0.025% trypsin-0.02% EDTA in HEPES buffered saline (50 mM HEPES, 150 mM NaCl, pH 7.4) and passaged after 5–7 d.

RT-PCR of TAFI

Adipose tissue was taken from a patient undergoing surgery after getting written informed consent. Total RNA from adipose tissue, HepG2 cells and HUVECs was prepared by the guanidine isothiocyanate procedure using Trizol Reagent (Life Technologies, Inc., Grand Island, NY). Five micrograms of total RNA were reverse transcribed to cDNA using a random primer, and cDNA was amplified by PCR. The RT-PCR was performed using the Superscript Preamplification system kit (Life Technologies, Inc., Gaithersburg, MD) following the manufacturer’s instructions. The sequences of the primers used for human TAFI cDNA amplification were 5′TCCAGCCCTCATCTCTCG-3′ corresponding to 431–454 nucleotides and 5′GGTAGAAGACGGTTTGTTG3′ corresponding to 451–454 nucleotides and 5′GGGAGAGTTTGTTGCGGATGAA3′. RT-PCR was performed with 35 cycles, denaturation at 94 °C for 30 sec, annealing at 52 °C for 1 min, and elongation at 72 °C for 1 min. The PCR product was cloned by the TA cloning method using the TOPO TA cloning kit (Invitrogen, San Diego, CA) following the manufacturer’s
instructions. Clones that contained inserts were selected for mini-preparation and digested with BstXI. The sequence of the double stranded BstXI cDNA fragment was performed using the dye terminator cycle sequencing FS ready reaction kit and ABI 373A DNA sequencer. The BstXI fragment of TAFI cDNA was then labeled with [α-32P]deoxy-CTP using a BcaBest labeling kit (Takara Shuzo, Tokyo, Japan).

**Statistical analysis**

Data are expressed as the mean ± SEM unless otherwise specified. The difference between the mean of two variables was calculated by the unpaired t test or by the Mann-Whitney U test as appropriate. ANOVA was employed for calculating the difference among the means of three or more variables. Univariate and multivariate analyses were performed to evaluate the relation of TAFI with markers of insulin resistance and obesity. A software package for the Macintosh (Statview 5.0, Abacus Concepts, Inc., Berkeley, CA) was employed for statistical analysis. A P value less than 0.05 was considered as statistically significant.

**Results**

TAT, a marker of coagulation activation, was significantly increased (27.1 ± 3.1 vs. 9.4 ± 1.0 nmol/liter; P < 0.05) in patients with type 2 DM (n = 57) compared with all healthy subjects (n = 30). The ratio between the plasma levels of DD and TAT complex (DD/TAT), an index of fibrinolytic activity, was significantly decreased (P < 0.05) in DM patients (15.5 ± 1.2) compared with nonobese healthy controls (26.5 ± 9.7). These findings demonstrate the occurrence of hypercoagulability and hypofibrinolysis in patients with type 2 DM. The antigen level and the activity of TAFI were significantly (P < 0.05) higher in plasma of patients with diabetes compared with normal controls (Fig. 1). Further, the plasma levels of TAFI antigen and DD were inversely and significantly (r = −0.5, P < 0.0002) correlated in all diabetic patients. These observations support the role of TAFI in the mechanism of diabetes-associated hypofibrinolysis. An inhibitor of activated TAFI is activated protein C (20). The plasma level of the marker of protein C generation, activated protein C-protein C inhibitor complex, was significantly increased (3.4 ± 0.2 vs. 1.9 ± 0.3 nmol/liter; P < 0.05) in DM patients compared with healthy subjects, and it was significantly and proportionally correlated (r = 0.6, P < 0.0001) with the plasma level of TAFI in all diabetic patients.

An abnormal condition frequently associated with type 2 DM is obesity (21). To study the role of obesity in the imbalance between coagulation and fibrinolysis, we categorized our DM patients in obese and nonobese groups. As described in Table 1, the visceral and sc fat areas, the serum insulin levels, the plasma levels of TAT were significantly increased, and GIR, a marker of insulin resistance, was significantly decreased in obese diabetic patients compared with nonobese patients. The activity and circulating levels of TAFI (Fig. 2) were significantly elevated, whereas the DD/TAT ratios were markedly decreased, in obese DM patients (11.3 ± 1.4) compared with nonobese DM patients (17.3 ± 11.3). On the other hand, the antigen level of TAFI (142.1 ± 100.8) compared with normal controls (26.5 ± 9.7). These findings demonstrate the occurrence of hypercoagulability and hypofibrinolysis in patients with type 2 DM. The antigen level and the activity of TAFI were significantly (P < 0.05) higher in plasma of patients with diabetes compared with normal controls (Fig. 1). Further, the plasma levels of TAFI antigen and DD were inversely and significantly (r = −0.5, P < 0.0002) correlated in all diabetic patients. These observations support the role of TAFI in the mechanism of diabetes-associated hypofibrinolysis. An inhibitor of activated TAFI is activated protein C (20). The plasma level of the marker of protein C generation, activated protein C-protein C inhibitor complex, was significantly increased (3.4 ± 0.2 vs. 1.9 ± 0.3 nmol/liter; P < 0.05) in DM patients compared with healthy subjects, and it was significantly and proportionally correlated (r = 0.6, P < 0.0001) with the plasma level of TAFI in all diabetic patients.

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**TABLE 1.** Clinical and laboratory profile of type 2 DM patients and healthy subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>DM patientsa</th>
<th>Healthy subjectsb</th>
</tr>
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<tr>
<td></td>
<td>Non-obese</td>
<td>Obese</td>
</tr>
<tr>
<td></td>
<td>patients</td>
<td>patients</td>
</tr>
<tr>
<td>Age (yr, mean ± SD)</td>
<td>56.1 ± 12.3</td>
<td>55.5 ± 10.8</td>
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<tr>
<td>Duration of disease (yr)</td>
<td>9.3 ± 1.1</td>
<td>8.1 ± 1.6</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>20.9 ± 0.3</td>
<td>26.2 ± 0.4a</td>
</tr>
<tr>
<td>Visceral fat (cm²)</td>
<td>73.4 ± 7.7</td>
<td>133.0 ± 10.0c</td>
</tr>
<tr>
<td>Subcutaneous fat (cm²)</td>
<td>97.3 ± 7.4</td>
<td>189.3 ± 19.8</td>
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<tr>
<td>Fasting serum insulin (pmol/liter)</td>
<td>30.0 ± 2.4</td>
<td>43.2 ± 4.2c</td>
</tr>
<tr>
<td>Glucose infusion rate (μmol/kg/min)</td>
<td>39.9 ± 1.9</td>
<td>32.9 ± 3.0e</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/liter)</td>
<td>8.7 ± 0.3</td>
<td>8.0 ± 0.5</td>
</tr>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>9.2 ± 0.3</td>
<td>9.1 ± 0.4</td>
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<tr>
<td>Systolic blood pressure (kPa)</td>
<td>17.5 ± 0.4</td>
<td>18.2 ± 0.3</td>
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<tr>
<td>Diastolic blood pressure (kPa)</td>
<td>10.1 ± 0.2</td>
<td>10.5 ± 0.2</td>
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<tr>
<td>Thrombin-antithrombin complex (nmol/liter)</td>
<td>23.4 ± 3.1</td>
<td>31.2 ± 4.1c</td>
</tr>
</tbody>
</table>

a All DM patients were being treated with diet alone with or without exercise therapy, but none of them has received oral hypoglycemic agents.

b All healthy subjects showed a normal oral glucose tolerance test.

P < 0.05, compared with nonobese DM patients.

c P < 0.05, compared with nonobese healthy subjects.

d P < 0.05, compared with nonobese healthy subjects.
These results suggest that increased circulating levels of TAFI may be an important mechanism of hypofibrinolysis in obesity.

Obesity is a well-known causative factor of insulin resistance. In the present study, the plasma levels of TAFI were independently and significantly correlated with the indicators of obesity, BMI and visceral fat area, with the marker of glucose intolerance, HbA1C, and with the indicator of insulin resistance, GIR (Table 2). GIR was significantly correlated with the plasma concentration of TAFI in both obese (r = −0.6, P = 0.01) and nonobese (r = −0.4, P = 0.02) DM patients (Fig. 3). Under normal conditions, the liver has been reported to be the main source of TAFI (22); in addition to the liver, in the present study, we demonstrated TAFI gene expression in human adipose tissues and in HUVECs (Fig. 4), suggesting that adipocytes and endothelial cells may be the source of increased circulating levels of TAFI and a cause of hypofibrinolysis in DM and/or obesity.

![Image](https://example.com/image.png)

**Fig. 2.** TAFI in obese patients with type 2 DM. The levels and the activity of TAFI in plasma were significantly elevated in obese DM patients (n = 18) compared with nonobese DM patients (n = 39) and nonobese healthy subjects (n = 20). The plasma levels of TAFI and the activity of TAFI in plasma were significantly elevated in nonobese DM patients compared with nonobese healthy subjects. *, P < 0.05, compared with nonobese DM patients and nonobese healthy subjects. #, P < 0.04, compared with nonobese healthy subjects.

**TABLE 2.** Results of the univariate and multivariate analysis with TAFI as the dependent variable

<table>
<thead>
<tr>
<th>Independent (X) variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>P values</td>
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<tr>
<td>Age</td>
<td>0.04</td>
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<tr>
<td>BMI</td>
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<td>SC fat</td>
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<tr>
<td>Fasting plasma glucose</td>
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<td>0.04</td>
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<tr>
<td>Hemoglobin A1C</td>
<td>0.29</td>
<td>0.02</td>
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<tr>
<td>Fasting serum insulin</td>
<td>0.33</td>
<td>0.03</td>
</tr>
<tr>
<td>Glucose infusion rate</td>
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</tr>
<tr>
<td>Duration of disease</td>
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**Discussion**

The fibrinolytic pathway is an important regulator of the coagulation cascade. A balance between the fibrinolysis and coagulation pathways is necessary for avoiding excessive bleeding during injury, and to maintain blood fluidity within the vascular system. Hypofibrinolysis is an important cause of hypercoagulability in diabetes (9). In support of this, we found in our DM patients high plasma concentrations of the clotting activation marker TAT and decreased concentration of the fibrinolysis index DD/TAT ratio. A pivotal event that controls the coagulation/fibrinolysis balance in vivo is the binding of thrombin to thrombomodulin on the vascular endothelial cell surface (23). The thrombomodulin-thrombin complex may exert anticoagulant activity by catalyzing the conversion of protein C to activated protein C, which down-regulates coagulation activation by inactivating factor Va and factor VIIIa (23). On the other hand, the thrombomodulin-thrombin complex may also promote coagulation by activating TAFI, which is a potent inhibitor of fibrinolysis (24, 25). Activated TAFI inhibits fibrinolysis by removing C-terminal lysine residues, which are high-affinity binding sites for plasminogen, from partially degraded fibrin (26) In the current study, we found that both the antigen levels and activity of TAFI are significantly increased and that they are significantly correlated with the circulating levels of DD in plasma of patients with type 2 DM. These results indicate the role of TAFI in the mechanism of hypofibrinolysis in DM patients. In this study, we also showed expression of TAFI in HUVECs, suggesting that secretion from endothelial cell may be the potential explanation for the increased circulating levels of TAFI in nonobese DM patients.

Another condition that is also frequently associated with hypofibrinolysis is obesity (17) Obesity is a predisposing factor for the development of type 2 DM and a risk factor for cardiovascular disease in diabetic and nondiabetic patients (17, 21). Several experimental and clinical observations implicated excessive secretion of PAI-1 by adipocytes in the mechanism of hypofibrinolysis associated with obesity (27) High content of PAI-1 has been described in murine epididymal fat pad, and mice with genetic obesity have increased PAI-1 expression in adipose tissue and in plasma (28, 29) In addition, clinical studies demonstrated that weight loss in obese subjects leads to significantly reduced plasma PAI-1 levels (29). In the present study, we raised the question of whether obesity is also associated with increased circulating levels of TAFI antigen in patients with type 2 DM. The results
showed that obese DM subjects have markedly increased activity and circulating levels of TAFI compared with nonobese DM patients and nonobese healthy individuals. The demonstration of increased gene expression of TAFI in human adipose tissue suggests that overproduction by adipocytes may be the cause of increased circulating level of TAFI in diabetic patients with obesity. To further clarify the role of obesity and insulin resistance in the increased circulating levels of TAFI in these patients, correlation of TAFI with various markers of DM and obesity was assessed. TAFI was independently and significantly correlated with markers of obesity (BMI, visceral fat area), glucose intolerance (HbA1c), and insulin resistance (GIR), suggesting that insulin resistance and obesity play important roles in the increased circulating level of TAFI in type 2 DM patients.

In brief, this study showed that increased circulating level of TAFI may be an important causative factor of hypofibrinolysis in patients with type 2 diabetes, obesity, and insulin resistance. Decreased fibrinolytic function is a condition that frequently results in recurrent or persistent thrombosis. Elucidation of mechanisms by which insulin resistance induces hypofibrinolysis may facilitate development of specific therapeutic interventions designed to attenuate the occurrence of vascular complications in diabetes. Such novel therapeutic interventions offer promise for decreasing atherogenesis and thereby improving the life expectancy in type 2 DM patients.

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