# Mechanism on Disorders of Coagulation and Fibrinolysis in Diabetes

**Tamotsu Matsuda, Eriko Morishita, Hiroshi Jokaji, Hidesaku Asakura, Masanori Saito, Tomotaka Yoshida, and Ken-ichi Takemoto**

**Determination of various important parameters of coagulation and fibrinolysis, clinical characteristics, and levels of serum lipid were compared in 193 patients with NIDDM and 50 control subjects. Levels of fibrinogen, tissue factor pathway inhibitor (TFPI), thrombin-antithrombin complex, and plasminogen activator inhibitor 1 in plasma increased significantly in the diabetic patients. Levels of TFPI correlated significantly with levels of total cholesterol. In the patients with coronary heart disease or cerebral infarction, levels of lipoprotein(a) increased significantly. From these results, we have concluded that there is a thrombotic tendency or at least an imbalance between the hemostatic and thrombosis-protecting system in diabetic patients, especially in patients with angiopathy.** *Diabetes* **45 (Suppl. 3):S109–S110, 1996**

In patients with diabetes, vascular complications such as myocardial infarction and cerebral infarction are important. Hypercoagulability in a broad sense, including enhanced platelet function and impaired fibrinolysis, may play a critical role in the pathogenesis of atherogenesis and thrombosis in diabetic patients. The purpose of this study was to clarify whether hypercoagulability exists in patients with diabetes.

## PLATELET FUNCTION IN DIABETIC PATIENTS

In the platelet system in diabetic patients, hyperaggregability (1–5) and an increase in plasma levels of von Willebrand factor (2,6–9), which is important in the adhesion of platelets to subendothelial cells, have been reported. In diabetic patients, elevation of levels of β-thromboglobulin and platelet factor 4 released from α-granules of platelets when platelets are activated has also been described (10–13). Recently, enhanced biosynthesis of thromboxane in platelets, which enhances thrombotic tendency (14), has been reported.

## COAGULATION FACTORS IN DIABETIC PATIENTS

We studied disorders of coagulation and fibrinolysis in patients with NIDDM. Clinical characteristics and levels of serum lipid were compared in 193 diabetic patients and 50 control subjects in our study (15). There were no statistically significant differences in sex and BMI, except age, triglyceride levels, and HDL cholesterol levels between the two groups.

In previous reports, increases in the levels of factors VII, VIII, and fibrinogen in diabetic patients have been noted (2,6–9,12,16). We also found that plasma fibrinogen content is significantly higher in patients with diabetes (15), although differences in age may affect the difference in fibrinogen level.

## PHYSIOLOGICAL INHIBITORS OF BLOOD COAGULATION IN DIABETIC PATIENTS

Regarding physiological inhibitors of blood coagulation in plasma, controversy exists (6,8,12,16). There is a possibility that glycosylation of some coagulation inhibitors in diabetic patients may impair the function of these inhibitors and cause hypercoagulability (17,18). However, our investigation revealed that activities of antithrombin III and protein C in the plasma of the diabetic patients did not differ from the control subjects (15).

Tissue factor pathway inhibitor (TFPI) is the most recently discovered inhibitor of blood coagulation. When the coagulation system is activated and activated factor X (Xa) is formed, TFPI combines Xa and neutralizes the activity of Xa. Moreover, the complex of TFPI and Xa inhibits the activity of the complex of activated factor VII and tissue factor, which triggers the coagulation cascade. In diabetic patients, the levels of TFPI in plasma were significantly higher than those of the control subjects (15). There was weak but significant positive correlation between the levels of TFPI and total cholesterol (15). This result could be due to the fact that TFPI combines with cholesterol. Therefore, it is possible that elevated levels of TFPI in the hypercholesterolemic patients may neutralize the thrombotic tendency in these subjects. However, another interpretation of this result may be possible. Tissue factor functions on the vascular surface and activates the coagulation cascade. Because TFPI inhibits tissue factor, it is reasonable to consider that TFPI acts mainly on the surface of the vessel wall, where this inhibitor is formed and released. Therefore, there is a possibility that an increase of TFPI in blood may reflect the release of this inhibitor from endothelial cells as a result of damage. Such a discussion is similar to the case of elevated levels of thrombomodulin, which is also an inhibitor of coagulation and formed in endothelial cells.

From the Department of Internal Medicine (III) (T.M., E.M., H.J., H.A., M.S.), Kanazawa University School of Medicine, and Central Clinical Laboratory (T.Y., K.-I.T.), Kanazawa University Hospital, Kanazawa, Japan.

Address correspondence and reprint requests to Dr. Tamotsu Matsuda, Takaramachi 13-1, Kanazawa University School of Medicine, Kanawaza, Japan.

Accepted for publication 30 November 1995.

Lp(a), lipoprotein(a); PAI-1, plasminogen activator inhibitor 1; TAT, thrombin-antithrombin complex; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator; Xa, activated factor X.

## IN VIVO ACTIVATION OF CLOTTING SYSTEM IN DIABETIC PATIENTS

Thrombin-antithrombin complex (TAT) in plasma reflects the amount of thrombin formed in the blood vessels and so an increase in this complex suggests the activation of the coagulation cascade in the bloodstream. A significant increase in TAT was observed in the diabetic patients (15), in whom levels of TAT in plasma were significantly higher in the patients with coronary heart disease. From these results, it is possible that hypercoagulability or damage to vessel walls, which activates the coagulation cascade, exists in these cases.

## FIBRINOLYSIS IN DIABETIC PATIENTS

Decreased levels of tissue plasminogen activator (tPA), which triggers activation of fibrinolytic system, have been reported in diabetic patients (2,19); however, the levels were higher in the diabetic patients in this study (15), although the difference was not statistically significant.

Regarding the physiological inhibitors of fibrinolysis, it has been postulated that an increase in plasma levels of plasminogen activator inhibitor 1 (PAI-1), which inhibits tissue plasminogen activator, is important in the development of thrombosis. In diabetic patients, it has been reported that PAI-1 is increased (20,21). In our study, a significantly higher level of PAI-1 was observed. In our previous study, levels of PAI-1 significantly correlated with those of triglyceride in the hyperlipidemic patients; however, a significant correlation was not observed in the diabetic patients.

Therefore, it is reasonable to consider that in diabetic patients, there is an imbalance between tPA and PAI-1, which causes thrombotic tendency in some diabetic patients.

Recently, it has been established that an increase in levels of lipoprotein(a) [Lp(a)] in plasma is an independent risk factor of atherosclerosis. Lp(a) has a binding domain homologous to that of plasminogen, the activation of which causes fibrinolysis. Therefore, it is possible that an increase of Lp(a) impairs fibrinolysis by competitive inhibition of plasminogen binding to the fibrin surface or endothelial cells of vessel walls, resulting in a thrombotic tendency. Regarding the microangiopathic complications of diabetes, the levels of Lp(a) are significantly higher in diabetic patients with retinopathy or nephropathy (data not shown). In our study, the levels of Lp(a) in diabetic patients were significantly higher in the patients with coronary heart disease or cerebral infarction than in the patients without macroangiopathy (15).

## REFERENCES


1. di Minno G, Silver MJ, Cerbone AM, Riccardi G, Rivellese A, Mancini M, Thiagarajan P: Increased binding of fibrinogen to platelets in diabetes; the role of prostaglandins and thromboxane. *Blood* 65:156–162, 1985
2. Garcia F, de la Calle H, Alava I, Navarro JL, Creighton LJ, Gaffney PJ: Diabetes mellitus as a hypercoagulable state; its relationship with fibrin fragments and vascular damage. *Thromb Res* 47:533–540, 1987
3. Cho NH, Becker D, Dorman JS, Wolfson LF, Kuller LH, Drash AL, Follansbee WF, Kelsey SF, Orchard TJ: Spontaneous whole blood platelet aggregation in insulin-dependent diabetes mellitus; an evaluation in an epidemiologic study. *Thromb Haemostasis* 61:127–130, 1989
4. Shukla SD, Paul A, Klachko DM: Hypersensitivity of diabetic human platelets to platelet activating factor. *Thromb Res* 66:239–246, 1992
5. Malyszko J, Urano T, Knofler R, Taminato A, Yoshimi T, Tanaka Y, Takada A: Daily variations of platelet aggregation in relation to blood and plasma serotonin in diabetes. *Thromb Res* 75:569–586, 1994
6. Christe M, Fritschi J, Lämmle B, Tran TH, Marbet GA, Berger W, Duckert F: Fifteen coagulation and fibrinolysis parameters in diabetes mellitus and in patients with vasculopathy. *Thromb Haemostasis* 52:138–143, 1984
7. v. d. Knaap JH, de Boer AC, Pannebakker MAG, van Heerde W, den Ottolander GJH: The effect of diabetes regulation on platelet release, fibrinolysis and coagulation tests, before and after stimulation with DDAVP. *Thromb Haemostasis* 53:118–125, 1985
8. Landgraf-Leurs MMC, Ladik T, Smolka B, Bock T, Schramm W, Spannagl M, Landgraf R: Increased thromboplastic potential in diabetes; a multifactorial phenomenon. *Klin Wochenschr* 65:600–606, 1987
9. Miller ME, Anagnostou AA, Ley B, Marshall P, Steiner M: Effect of fish oil concentrates on hemorheological and hemostatic aspects of diabetes mellitus; a preliminary study. *Thromb Res* 47:201–214, 1987
10. Sacchi S, Curci G, Piccinini L, Messerotti A, Roncaia R, Bendetti PG: Platelet α granule release in diabetes mellitus. *Scand J Clin Lab Invest* 45:165–168, 1985
11. Rosove MH, Frank HJL, Harwig SSL, Berliner J: Plasma β- thromboglobulin is correlated with platelet adhesiveness to bovine endothelium in patients with diabetes mellitus. *Thromb Res* 37:251–258, 1985
12. di Mario U, Borsey DQ, Contreas G, Prowse CV, Clarke BF, Andreani D: The relationship of soluble immune complexes, insulin antibodies and insulin-anti-insulin complexes to platelet and coagulation factors in type diabetic patients with and without proliferative retinopathy. *Clin Exp Immunol* 65:57–68, 1986
13. Maiello M, Boeri D, Bonadonna R, Odetti P, Saccarello A, Adezaati L: Platelet and clotting activities after cold stress in diabetic patients. *Thromb Res* 50:885–894, 1988
14. Davi G, Ptrono C, Catalano I, Custo C, Giammarresi C, Ganci A, Cosentino F, Notarbartolo A: Inhibition of thromboxane biosynthesis and platelet function by indobufen in type II diabetes mellitus. *Arterioscler Thromb* 13:1346–1349, 1993
15. Morishita E, Asakura H, Jokaji H, Saito M, Uotani C, Kumabashiri I, Yamazaki M, Aoshima K, Hashimoto T, Matsuda T: Hypercoagulability and high lipoprotein(a) levels in patients with type II diabetes mellitus. *Atherosclerosis* 120:7–14, 1996
16. Ktoczko J, Wojtukiewicz M, Bielawiec M, Zarzycka, Kinalska I: Plasma factor XIII and some other haemostasis parameters in patients with diabetic angiopathy. *Acta Haematol* 76:81–85, 1986
17. Ceriello A, Dello Russo P, Zuccotti C, Florio A, Nazzaro S, Pietrantuono C, Rosato GB: Decreased antithrombin III activity in diabetes may be due to non-enzymatic glycosylation; a preliminary report. *Thromb Haemostasis* 50:633–634, 1983
18. Duboscq C, Quintana I, Barros J, Kordich L: Heparin cofactor II in diabetic patients. *Blood Coagul Fibrinolysis* 5:201–204, 1994
19. Juhan-Vague I, Vague P, Poisson C, Aillaud MF, Mendez C, Collen D: Effect of 24 hours of normoglycaemia on tissue-type plasminogen activator plasma levels in insulin-dependent diabetes. *Thromb Haemostasis* 51:97–98, 1984
20. Juhan-Vague I, Roul C, Alessi MC, Ardissone JP, Heim M, Vague P: Increased plasminogen activator inhibitor activity in non insulin dependent diabetic patients — relationship with plasma insulin. *Thromb Haemostasis* 61:370–373, 1989
21. Schneider DJ, Nordt TK, Sobel BE: Attenuated fibrinolysis and accelerated atherogenesis in type II diabetic patients. *Diabetes* 42:1–7, 1993