Letter to the Editor

Received: July 27, 1991

Received in revised form: October 8, 1991

Accepted: October 10, 1991

Haemostasis 1992;22:50-51

Increased Prothrombin Fragment 1 +2 in Type I Diabetic Patients

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The pathogenesis of vascular lesions in diabetic patients has been considered to be at least partly dependent on the alterations in the hemostatic system [1]. However, the existence and the relevance of a hypercoagulable state in diabetes mellitus have been the subject of much debate [1,2].

It has been demonstrated that the conversion of the coagulation zymogen prothrombin to thrombin is associated with the prominent production of a cleavage product namely prothrombin fragment 1+2 (F1+2) [3]. It has been proposed recently that prothrombin F1+2 plasma levels may be considered a very sensitive marker for hypercoagulable states in humans [4].

We evaluated prothrombin F1+2 (ELISA) levels in 19 insulin-dependent diabetic patients without signs of vascular complications (12 males and 7 females: age 23.4 ± 1.9 years, mean $\pm$ SE; body mass index 22.8 ± 1.4 ; duration of diabetes 6.4 ± 1.3 years; insulin regimen 25-55 U/day, mean 32.8 ± 2.5 U/day; all subjects had 24-hour urinary albumin excretion rates less than $30 \mu\text{g/min}$, and no

microaneurysms were detected on full fundal photographs or fluorescein fundal angiography; they had systolic blood pressures < 120 mm Hg and diastolic blood pressures < 90 mm Hg; ischemic heart disease and peripheral vascular occlusion were excluded according to local criteria) compared to 10 matched healthy normal subjects (6 males and 4 females: age 24.2 ± 1.8 years, body mass index 23.2 ± 1.3).

Prothrombin F1+2 levels were significantly elevated in diabetic patients (0.69 ± 0.11 vs. 0.27 ± 0.03 nmol/l; $p < 0.01$), but no correlation was found between prothrombin F1+2 plasma levels and both fasting glycemia ($r = 0.17$) and glycosylated Hb A1c ($r = 0.16$).

Increased FPA levels have been reported in diabetes [5]. These findings were considered more suggestive of a thrombin hyperactivity than of an increase of thrombin production [6]. This hypothesis was sustained by the evidence of normal [7] or depressed [6] levels of thrombin-antithrombin complex in the presence of increased FPA [6] and fibrin monomers [7] in diabetes.

We demonstrated that diabetic patients may have an increased thrombin production. These data are consistent with the presence of a relative hyperactivatable factor X in diabetes [8] which might explain a thrombin overproduction. Our data, moreover, support the evidence that there may be a hypercoagulable state in diabetes, even in the absence of vascular complications.

References

- Jones RL, Peterson CM: The fluid phase of coagulation and the accelerated atherosclerosis of diabetes mellitus. *Diabetes* 1981;30:(suppl 2):33-38.
- Ostermann H, van de Loo: Factors of the hemostatic system in diabetic patients. A survey of controlled study. *Haemostasis* 1986; 16:386-416.
- Rabie MJ, Blashill A, Furie B, Furie BC: Prothrombin fragment 1.2.3, a major product of prothrombin activation in human plasma. *J Biol Chem* 1986;261:13210-13215.
- Bauer KA, Rosenberg RD: The pathophysiology of the prethrombotic state in humans: Insights gained from studies using markers of hemostatic system activation. *Blood* 1987;70:343-350.
- Jones RL: Fibrinopeptide A in diabetes mellitus: Relation to levels of blood glucose, fibrinogen disappearance, and hemodynamic changes. *Diabetes* 1985;34:836-843.
- Ceriello A, Guigliano D, Quatraro A, Marchi E, Barbanti M, Lefebvre PJ: Evidence for a hyperglycaemia-dependent decrease of antithrombin-thrombin complex formation in humans. *Diabetologia* 1990;33: 163-167.
- Van Wersch JWJ, Westerhuis LWJJM, Venekamp WJRR: Coagulation activation in diabetes mellitus. *Haemostasis* 1990;20:263-269.
- Ceriello A, Quatraro A, Marchi E, Barbanti M, Dello Russo P, Lefebvre PJ: The role of hyperglycaemia-induced alterations of anti-thrombin III and factor X activation in the thrombin hyperactivity of diabetes mellitus. *Diabet Med* 1990; 7:343-348.