Comment on 'Glycometabolic Control and Fibrinolysis in Diabetic Patients' by van Wersch et al.

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Dear Editor,

We read the article entitled 'Glycometabolic Control and Fibrinolysis in Diabetic Patients', published in Haemostasis [1]. In this study, D-dimer (DD) and plasminogen activator inhibitor (PAI) levels were studied in 148 diabetic patients and it was found that DD decreases and PAI increases with worsening glycometabolic control. Based on these findings, it was suggested that fibrinolysis decreases in badly controlled diabetes mellitus. But, in our opinion, there are some important pitfalls in the study. First of all, only DD and PAI levels are not enough to comment on the rate of fibrinolysis, which is tightly controlled by the balance of the activators [tissue-plasminogen activator (tPA) and urokinase] and inhibitors (α₂-antiplasmin, PAI-1) [2]. This scheme is much more complicated with the inhibition of PAI-1 by protein C [3]. Thus, individual levels of any of the aforementioned parameters give no information on the mode of action of the fibrinolytic system. The net result of these complex interactions is reflected and may be measured by the euglobulin lysis time assay [4], which was not performed in the above-mentioned study.

Secondly, the mean age of the patients is 56.4 years, and is apparently older than the control group, whose mean age has not been stated, but the reported age range was 24–50 years. Age-matching of study groups is essential when studying fibrinolysis, particularly tPA and PAI-1 [5]. It was also confirmed in this study that PAI levels increase with age, as well as DD levels. Therefore, the statement that '30.8% and 22.4% of the DD and PAI levels, respectively, are beyond the upper reference level' has no statistical meaning. Multivariate regression analysis should have been performed instead of simple linear regression analysis in order to overcome this mismatching.

Thirdly, a significant negative correlation of DD with HbA_{1c} but no correlation with HbA_{1c} had been found; the authors have attempted to explain this discrepancy by the technical difficulties and low reliability of the HbA_{1c} assay. On the other hand, a significant positive correlation between PAI and HbA_{1c} levels has been firmly relied on. If the HbA_{1c} assay of the study was unreliable, then the latter finding should not be interpreted as important despite the statistical significance, which had been also attained by

van Hinsberg VWM, Bertina RM, van Wijn-gaarden A, van Tilburg NH, Emeis JJ, Haverkate F: Activated protein C decreases plasminogen activator-inhibitor activity in endothelial-cell conditioned medium. *Blood* 1985;65:444–451.

Urano T, Sakakibara K, Rydzewski A, Urano S, Takada Y, Takada A: Relationships between euglobulin clot lysis time and the plasma levels of tissue plasminogen activator and plasminogen activator inhibitor 1. *Thromb Haemostas* 1990;64: 82–86.

Hashimoto Y, Kobayashi A, Yamazaki N, Suga-wara Y, Takada Y, Takada A: Relationship between age and plasma t-PA, PA-inhibitor and PA activity. *Thromb Res* 1987;46:625–633. simple regression analysis, not by multivariate regression analysis.

If this study had been designed longitudinally, such as comparison of DD and PAI levels of the same individuals with and without good glycometabolic control, then some valid suggestions about fibrinolysis in diabetic patients could have been made. The only valid conclusion which can be derived from this study, designed in the presented manner, is that ‘DD and PAI levels increase with age in diabetic patients’.

References

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