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Fibrinogen, fibrinolysis and diabetes mellitus: a comment

P. Vague, I. Juhan-Vague

Diabetes Department and Haemostasis Laboratory, University Hospital Timone, Marseille, France

Disturbances of the haemostatic system are well-identified risk factors for coronary heart disease. As diabetic individuals are particularly prone to coronary atherosclerosis, in this issue of *Diabetologia* Dr. Ceriello and Dr. Morale et al. address the question of the involvement of the haemostatic system in diabetes mellitus. They discuss the potential usefulness of intervention trials, and focus on the well-known or most-studied parameters, i.e. excess of plasma fibrinogen and defective fibrinolysis. They present justified arguments resulting from human and animal in vivo and in vitro studies to discuss the pros and cons of therapeutic intervention. Rather than question their view point, we would like to comment, with a more clinical perspective. In this respect two questions may clarify the problem:

– Among diabetic patients are fibrinogen and fibrinolysis abnormalities a mere sign of atherosclerosis, i.e. a risk marker associated with but not causally related to the risk, or are they a risk factor directly playing a role in the development of atherothrombotic lesions and subsequent cardiac events?

If they represent a risk factor what is the most efficient intervention? Is it preferable to prevent the haemostatic disturbances by treating their cause, to inhibit the synthesis and/or biological activity of fibrinogen, or that of the main regulator of the fibrinolytic process, plasminogen activator inhibitor-1 (PAI-1)?

Corresponding author: Professor Philippe Vague, Diabetes Department, University Hospital Timone, F-13385 Marseille Cedex 5, France

Abbreviations: PAI-1, Plasminogen activator inhibitor-1; tPA, tissue plasminogen activator; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

Many prospective studies have established that haemostatic disturbances, including excessive fibrinogen levels and low fibrinolytic activity (excessive PAI-1, tissue plasminogen antigen (tPA) levels), and elevated factor VII, von Willebrand factor, are associated with subsequent cardiac events [1–4]. Elevated fibrinogen levels [5] and impaired fibrinolysis [6, 7] are more common in diabetic patients than in non-diabetic control subjects. However, there is no consensus about the influence of diabetes per se on these abnormalities. Many factors, including age, smoking habits, BMI, fat distribution, sedentary lifestyle and microalbuminuria may influence the parameters of haemostasis and act as confounding factors.

On the other hand, although cardiovascular disease is not only frequent but also has a severe prognosis in insulin-dependent (IDDM) as well as in non-insulin-dependent (NIDDM) diabetic subjects, these two groups of patients must be clearly separated. Differences in age of onset and in the presence of insulin resistance preceding the appearance of NIDDM, itself a factor of atherothrombosis, would be the main reasons.

Fibrinogen and diabetes

In IDDM, three recent studies report the following results. El Khawand et al. [8] did not observe higher fibrinogen levels in diabetic patients than in non-diabetic subjects (304 vs 285 mg/dl). Diabetic individuals with HbA_{1c} levels lower than 8 % had normal fibrinogen levels while patients with poor metabolic control had elevated levels. Unlike the other haemostatic parameters, fibrinogen levels were related not to HbA_{1c} levels, but to microalbuminuria. In Ganda and Arkin's study [9] fibrinogen levels were slightly higher among IDDM patients than control subjects but the main factor responsible for excessive fibrinogen

levels was the presence of vascular complications. Among twin pairs discordant for IDDM, Dubrey et al. [10] noted that fibrinogen levels were 8% higher in the diabetic twin. Intra-pair correlations demonstrate the role of genetic factors in the control of fibrinogen levels.

Fibrinogen has been found to be elevated in NIDDM, according to some studies, although not in a recent study [11]. In NIDDM patients, high fibrinogen levels are closely related to advancing age or to the presence of vascular complications [10, 11]. Fibrinogen levels may also be related to the actual insulin resistance these patients present [12]. In non-diabetic subjects, a weak correlation has been observed with plasma insulin level [13–15], BMI [16], waist-to-hip ratio [17, 18], hyperlipidaemia [19], as well as hypertension [20], all parameters clustering in the insulin resistance syndrome. A role for non-esterified fatty acids (NEFA) has been suggested to explain the relationship of fibrinogen to insulin resistance because a joint increase in NEFA and fibrinogen is seen in a variety of clinical and experimental conditions [21].

Therefore, it seems diabetes itself is only minimally responsible for the high fibrinogen levels which may occur in diabetic patients. Various factors may play a role, especially the presence of vascular disease at a clinical or preclinical stage. And in fact a relationship has been well-established between plasma concentration of fibrinogen, the quantity of fibrinogen and fibrin present in the vessel wall, and the severity of arterial wall disease [22–24]. One must also keep in mind that plasma fibrinogen concentrations are influenced by many genetic as well as environmental factors. It is an acute phase protein and could be a marker of an inflammatory process. In this issue, Morale et al. point out the inflammatory reaction accompanying atherosclerosis.

Defective fibrinolysis and diabetes

It has been well-demonstrated that patients with coronary heart disease are characterized by a defective fibrinolytic system; but, the significance of these abnormalities as a risk factor in epidemiological studies has been controversial. While low fibrinolytic activity, PAI-1 activity, PAI-1 antigen, and tPA antigen are generally predictive of cardiac events in univariate analysis [25] this predictivity disappears or is strongly attenuated when other risk factors are taken into account [1, 4, 26], mainly excessive body weight, skinfold thickness, waist-to-hip ratio, blood pressure and low HDL cholesterol; all parameters of the plurimetabolic insulin resistance syndrome. Various lines of evidence allow us to include high PAI-1 levels as a facet of the insulin resistance syndrome strongly associated with BMI, the amount of visceral fat, and plasma insulin and triglyceride levels [12, 27]. Weight reduction, physical training, and metformin administration, all interventions aiming at reducing insulin resistance, decrease PAI-1 levels [27].

In IDDM patients, PAI-1 levels have not been found to be elevated in many studies [6, 28]. In NIDDM patients PAI-1 levels are frankly elevated [6, 7], but are in close relation with BMI, waist-to-hip ratio, plasma insulin and triglyceride levels and are poorly or not correlated with blood glucose or HbA_{1c} levels. High PAI-1 levels seem to depend more on the insulin resistance which precedes and accompanies NIDDM than on diabetes itself.

In conclusion, it is clear that disturbances of the haemostatic systems and especially high fibrinogen and PAI-1 levels may be found in diabetic patients, but it is uncertain whether they could result from chronic hyperglycaemia. In their pathogenesis a key role is probably played by the arterial wall status for the fibrinogen concentration, and the insulin resistance syndrome or its determinants, mainly the excess of visceral fat for the defective fibrinolysis.

As a group at risk for cardiovascular disease, diabetic patients could be good candidates for an intervention trial, but given the lack of evidence of a direct and important effect of diabetes on fibrinogen levels on the one hand, and the absence of specific pharmacological agents for lowering fibrinogen on the other, such intervention trials would be difficult to conduct. Dr. Ceriello states that this approach could not be used to test a causal relationship between fibrinogen and cardiovascular events in diabetic patients.

Involvement of elevated PAI-1 levels in the development of the atherosclerotic plaque and its complications is strongly suspected but not absolutely proven in humans. However, some animal studies are in favour of the pathogenic effect of defective fibrinolysis. Interesting results have been described recently in mice transgenic for the PAI-1 gene [29] or with the use of neutralizing monoclonal antibodies [30]. Before developing drugs able to counteract PAI-1 activity or to decrease its synthesis without undesirable side effects it is probably useful to test such molecules in animal models, to determine if an acute or chronic suppression of PAI-1 activity is beneficial.

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