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For debates

Fibrinogen and diabetes mellitus: is it time for intervention trials?

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During the past decade, the potential role of haemostatic factors, particularly fibrinogen, in atherosclerosis and its complications has gained considerable interest.

Since the early 1980s, several extensive prospective observational studies have convincingly demonstrated that fibrinogen is a powerful, independent marker for cardiovascular diseases in non-diabetic subjects [1], while our knowledge on the impact of fibrinogen as a cardiovascular risk factor in diabetes mellitus is still incomplete. Moreover, another important question is whether fibrinogen promotes atherosclerosis and cardiovascular diseases in diabetes, or does it increase in plasma due to the presence of atherothrombotic lesions.

Fibrinogen and diabetes

Atherosclerosis is accelerated in both insulin-dependent (IDDM) and non-insulin-dependent diabetes (NIDDM), and a 'hypercoagulable state' may be at least partly contributory [2]. In recent years, a growing number of studies has focussed attention on fibrinogen in diabetes, suggesting its role as a marker of cardiovascular risk also in this disease. An association between initial hyperfibrinogenaemia and the subsequent occurrence of macroangiopathy, as well as the evidence that a high fibrinogen concentration enhances the risk of cardiovascular disease in diabetic patients, have been reported [3–5]. The demonstration that diabetes and parental history of diabetes are strongly and positively associated with fibrinogen levels has also been made [6].

Hypercoagulability has been suggested to be a result rather than a cause of diabetic vascular disease. However, fibrinogen levels in IDDM patients without clinically demonstrable macroangiopathy are increased and are related to glycaemic control [7].

The relevance of fibrinogen as a cardiovascular risk factor in diabetes has been stressed by recent work on twins [8]. This study demonstrated the existence of similarities in cardiovascular risk factors in twins; however, only systolic blood pressure and fibrinogen were adversely affected by diabetes [8].

Of particular interest is the association between microalbuminuria and fibrinogen in diabetes. Microalbuminuria is associated with an increased risk of cardiovascular disease in diabetic patients [9]. Increased fibrinogen levels in the presence of microalbuminuria suggests that coagulation abnormalities might be part of the cardiovascular risk in microalbuminuric patients [10].

Evidence shows that in diabetic patients fibrinogen may be a cardiovascular risk factor because it is correlated to increased thrombin formation [11]. The existence of both increased fibrinogen and thrombin activation in diabetes has been hypothesized to play a role in the pathogenesis of atherosclerosis in this disease. Endothelial cell activation is accompanied by the appearance at the cell surface of adhesion molecules, whose function is to mediate the attachment of certain leukocytes [12]. Leukocyte-endothelial cell interaction may be important in atherogenesis, where an early step may be the binding and sub-endothelial cell migration of monocytes from the intima into the media of the blood vessel wall [13]. Integrin intercellular adhesion molecule-1 (ICAM-1) is involved in this mechanism [14]. A recent paper

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Abbreviations: ICAM-1, Intercellular adhesion molecule 1; IDDM, insulin-dependent diabetes; NIDDM, non-insulin-dependent diabetes.

reported that the soluble form of ICAM-1 is increased in the presence of vascular disease in non-diabetic subjects [15]. Fibrinogen acts as a bridge between activated leukocytes and ICAM-1 on the endothelial cell surface [14], while thrombin regulates the expression of this integrin [16]. A strong correlation between increased circulating ICAM-1 and both fibrinogen levels and thrombin formation suggests a possible link between coagulation derangement and atherosclerosis in diabetes [17].

Another important issue is the relationship between fibrinogen levels and hyperglycaemia. A significant correlation between fibrinogen and HbA_{1c} has been frequently found [11, 18]. These data are consistent with the evidence that improving metabolic control in both IDDM [19] and NIDDM [20] patients causes fibrinogen levels to fall. A recent study was not able to confirm this result [21]. However, there was a correlation between fibrinogen and HbA_{1c} both at the beginning and at the end of the study, when HbA_{1c} was significantly reduced [21].

Mechanisms increasing fibrinogen in diabetes. An increase in fibrinogen synthesis has been reported in diabetes [22]. Another finding in diabetic patients is an increased rate of fibrinogen clearance, with shorter fibrinogen circulating half-life [23]. This higher clearance rate means that synthesis is actually even more increased than suggested by the plasma level elevation.

Insulin resistance, which is common in NIDDM patients, is also accompanied by increased fibrinogen levels [24, 25].

Atherosclerosis bears similarities to an inflammatory process [26]. Both inflammation and atherosclerosis have been correlated to an existing 'oxidative stress' [27]. Oxidative stress, possibly generated either by hyperglycaemia [28] and/or insulin resistance [29], has been involved in the pathogenesis of macroangiopathy in diabetes [30].

A correlation between markers of the oxidative stress and fibrinogen has been reported in diabetic patients [31, 32]. Recently, the possibility that fibrinogen synthesis in both normal and diabetic subjects is modulated through a feedback pathway by thrombin activation has been suggested [11, 33, 34]. Since free radicals activate thrombin formation in diabetes [35], oxidative stress may represent a possible link between the diabetic state and hyperfibrinogenaemia (Fig. 1).

This suggests that a high level of fibrinogen in plasma might be a risk marker for cardiovascular disease because it reflects increased thrombin formation and therefore a greater probability that a thrombotic event will occur.

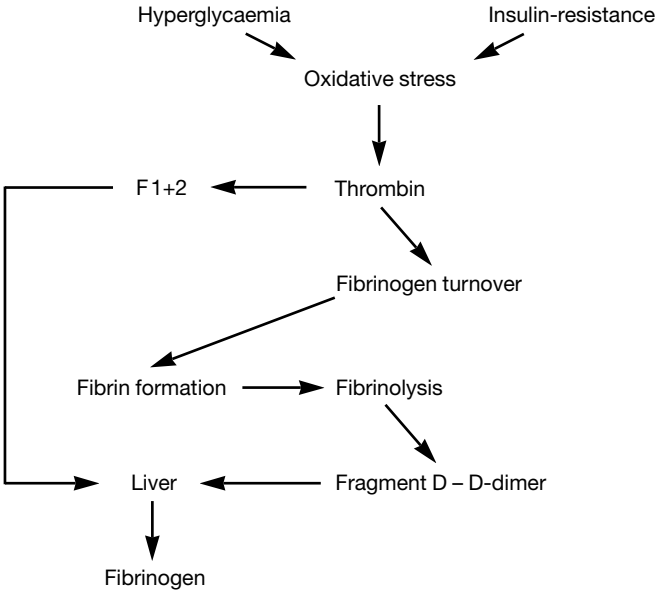

Fig. 1. Hypothetical pathways leading to increased fibrinogen plasma level in diabetes. Hyperglycaemia and insulin-resistance, and the consequent oxidative stress, may give rise to increased thrombin formation. This process causes increased production of prothrombin fragments (F1 + 2) (which are produced in quantities equimolar to the breakdown of thrombin) and increased turnover of fibrinogen, with increased production of fibrin and consequently increased release of fragment D (of which D-dimer is the plasma circulating expression). Both F1 + 2 and fragment D regulate the production of fibrinogen in the liver; increased release of them into the circulation may produce an increase in circulating fibrinogen

Conclusions: is it time for intervention trials?

Mounting data support the evidence that fibrinogen is a strong predictor of atherosclerotic cardiovascular disease in diabetes. Patients with diabetes have an excess mortality, predominantly due to cardiovascular disease. Therefore, it is reasonable to consider that fibrinogen may deserve inclusion in the 'cardiovascular risk profile' of diabetic patients.

Especially now that the international standardization of fibrinogen assays appears to be at hand [36], the scientific community claims that the time has come to test the hypothesis of fibrinogen as a cardiovascular risk factor by intervention trials. A lower plasma fibrinogen level can be achieved by reducing cigarette smoking [37], by exercise [38, 39] and in diabetic patients probably by improved metabolic control [19, 20]. Fibrinogen lowering can also be achieved by heparin [40] or low molecular weight heparin [41] administration. In diabetic patients these results were confirmed for both heparin formulations and moreover for the glucosaminoglycan sulodexide [42]. Glucosaminoglycans seem to be of particular interest, since an increasing number of studies elucidate their mechanism of action in lowering fibrinogen levels [43]. Fibrinogen can be decreased by drugs that

reduce hepatic fibrinogen synthesis: this group includes anabolic steroids, ticlopidine, pentoxifylline and the fibrates bezafibrate and fenofibrate [44]. Bezafibrate consistently lowers plasma fibrinogen levels by 10–20 % in both IDDM [45] and NIDDM patients [46], which represents a substantial potential reduction in primary and secondary cardiovascular risk according to epidemiological studies. Lowering fibrinogen, then, seems to be an attractive approach to cardiovascular disease prevention, even in diabetes. Fibrinogen reduction should be considered desirable in diabetic subjects, who are patients at high risk of arterial disease. This goal may be achieved either by lifestyle modification or by drugs acting on fibrinogen plasma level and factors that co-segregate with it. However, it is evident that none of the above-mentioned drugs and factors capable of lowering fibrinogen plasma level are specific in doing so, since all of them also modify other cardiovascular risk factors. Therefore, until we possess a drug that specifically reduces fibrinogen, we probably will not be able to definitely test whether there is a simple association or a causal relationship between fibrinogen and cardiovascular events, even in diabetes.

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