

Platelet adhesiveness, plasma fibrinogen, and fibrinolytic activity in juvenile-onset and maturity-onset diabetes mellitus

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SUMMARY The nature of vascular disease and its complications are different in juvenile-onset (JOD) and maturity-onset (MOD) diabetes mellitus. In order to explore the disturbances in the coagulation-fibrinolytic system, platelet adhesiveness, plasma fibrinogen, and euglobulin lysis time were estimated in 26 cases of JOD and 36 cases of MOD. Two groups of age- and sex-matched controls were also studied. Platelet adhesiveness and plasma fibrinogen were essentially normal while euglobulin lysis time was significantly decreased in the JOD group. The MOD group, on the other hand, showed a reversed pattern in the form of enhanced platelet adhesiveness and plasma fibrinogen and no compensatory increase in fibrinolysis.

Vascular disease plays a major role in diabetic morbidity and mortality. Microvascular disease is the predominant manifestation of juvenile-onset diabetes (JOD), while large-vessel atheroma is the major problem in the long-term survival of maturity-onset diabetics (MOD). Small and large vessel diseases are best considered as separate entities.^{1,2} There is no good evidence that interrelates the two conditions to a common pathology. Platelet, fibrinogen and other haemostatic abnormalities could be the link for small and large vessel disease in diabetics. The possibility of a hypercoagulable state and disturbances in the delicately balanced dynamic equilibrium between coagulation and fibrinolysis has been studied piecemeal, mainly in MOD, but with controversial results.³⁻⁶ This aspect has not been adequately explored in JOD. We have previously reported disturbances in this equilibrium in some clinical settings having thromboembolic complications as a major component of their natural history.⁷⁻¹⁰

The importance of the subject and a paucity of reports on JOD prompted this study. Platelet adhesiveness, plasma fibrinogen, and euglobulin lysis time were studied in 36 patients with MOD and in 26 patients with JOD. Equal numbers of age- and sex-matched controls were studied.

Material and methods

One hundred and twenty-four subjects were studied in the following groups:

Group A: 26 patients with JOD, mean age 18.2 (range 13-21) years.

Group B: 26 normal healthy controls, mean age 17.0 (range 13-19) years.

Group C: 36 patients with MOD, mean age 37.2 (range 28-50) years.

Group D: 36 normal healthy controls, mean age 35.5 (range 27-48) years.

The diagnosis was based essentially on clinical history, age at onset, blood sugar concentrations, and glucose tolerance studies. All were recently discovered new cases, and none was on any type of antidiabetic treatment at the time of this study.

Platelet adhesiveness was estimated by the method of Eastham¹¹ using adenosine diphosphate. Since many factors such as diet,¹² physical exertion,¹³ and smoking¹⁴ affect platelet adhesiveness, the procedure was standardised as rigidly as was practicable. Blood was collected using siliconised apparatus in the early morning after an overnight fast. Each subject abstained from smoking for at least 18 hours before venepuncture. Physical activity was reduced to a minimum in all the subjects.

Plasma fibrinogen was estimated by the method of Ratnoff and Menzie¹⁵ and euglobulin lysis time by

the method of Cash.¹⁶ Subjects were not given any drug known to interfere with the above estimations.

Results

Platelet adhesiveness, plasma fibrinogen, euglobulin lysis time, and the results of statistical analysis in respect of each group are shown in the Table. The mean platelet adhesiveness in groups A, B, C, and D was 48.7%, 51.3%, 62.2%, and 54.6%, respectively. There was no significant change of platelet adhesiveness in JOD (group A) as compared to the normals (group B). Patients with MOD (group C), on the other hand, showed significant platelet hyperadhesiveness ($p < 0.001$). Plasma fibrinogen was significantly increased ($p < 0.05$) in group C, while group A showed no significant change when compared with their respective control groups. Euglobulin lysis time was markedly decreased in group A, indicating a fairly active fibrinolytic activity. No such change in fibrinolysis was noted in patients with MOD (group C).

Measurements (mean \pm SD) of platelet adhesiveness (%), plasma fibrinogen (g/l), and euglobulin lysis time (min) in juvenile-onset (A) and maturity-onset (C) diabetes mellitus subjects and in normal controls (B and D)

Group	No. of subjects	Platelet (%) adhesiveness	Plasma (g/l) fibrinogen	Euglobulin lysis time (min)
A	26	48.7 \pm 8.8	2.9 \pm 1.5	240.5 \pm 98.4
B	26	51.3 \pm 8.9	2.5 \pm 1.0	312.5 \pm 52.5
C	36	62.2 \pm 9.7	3.2 \pm 1.7	295.2 \pm 105.2
D	36	54.6 \pm 4.6	2.6 \pm 0.9	328.3 \pm 64.2
p values				
A ν B		NS	NS	< 0.001
C ν D		< 0.001	< 0.05	NS

NS = not significant.

Discussion

Our data showed that factors that contribute to a hypercoagulable state, such as platelet hyperadhesiveness and increased plasma fibrinogen, are essentially normal in juvenile-onset diabetes. A marked variation in plasma fibrinogen in young diabetics, however, suggests a high value in some in the early stages but this change occurred in very few patients and did not affect the overall values materially. In addition, they have a fairly active fibrinolytic system at work. The picture is entirely different in maturity-onset diabetics. These patients show a hypercoagulable state, as indicated by a significant increase in platelet adhesiveness and plasma fibrinogen, which is not adequately compensated by an increase in fibrinolytic activity.

Significant variations as noted above in normal haemostasis may well explain, at least in part, the differences seen in the natural history of these conditions.

Recently clinical, biochemical, pathological, and immunological findings have led to the realisation that diabetes mellitus is a heterogeneous group of diseases rather than a single nosological entity. Despite recent advances in the understanding of the natural history of diabetes mellitus with a concurrent improvement in clinical management, vascular disease and thromboembolic disorders continue to play a major role in diabetic mortality and morbidity. Diabetic vascular disease is unique in having two equally important manifestations, disease of the small vessels, microangiopathy, and of the larger vessels (coronary, cerebral, and leg vessels) in the form of precocious atheroma. Small and large vessel diseases are best considered as separate entities. There is no good evidence that interrelates the two conditions to a common pathology. Platelet and fibrinogen abnormalities, for which there is now adequate evidence,^{1,3-6} could be the link between small and large vessel disease in diabetes, but other considerations, such as the incidence of the two vascular complications in young and middle-aged diabetics, suggest a different aetiology of small and large vessel syndromes. This is amply supported by the present study.

Platelets play a pivotal role in the development of precocious atheroma. Many platelet function defects have been described in MOD,^{3,5,6} and these may well initiate the vascular disease. The sequence postulated consists of endothelial damage, platelet adherence, platelet aggregation, smooth muscle proliferation, lipid accumulation, plaque formation, and, finally, thrombosis.¹⁷ Our findings are in agreement with those of others. This process is likely to be accentuated by hyperviscosity as a result of increased plasma fibrinogen (Table). Diminished fibrinolysis further accelerates the process. The picture is not very clear in juvenile-onset diabetes. The sequence of events leading to the microvascular disease is not well understood. Our data show that platelets and fibrinogen play no significant role in the process. This is also supported by the low incidence of precocious atherosclerosis in these patients. An active fibrinolytic system further helps in keeping the vascular channels clear. Our finding may have important clinical implications and suggests a definite role for drugs that reduce hypercoagulation and stimulate the fibrinolytic system in MOD. These agents are not likely to have a significant role in the JOD group. The validity of these findings can only be substantiated by more long-term control studies.

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