Coagulation Profile in Diabetes and its Association with Diabetic Microvascular Complications

Ritu Madan*, B Gupta**, Sumita Saluja***, UC Kansra***, BK Tripathi***, BP Guliani****

Abstract

Objectives: To investigate the haemostatic parameters and to assess their relationship with microvascular complications in type 2 diabetes mellitus.

Materials and Methods: Coagulation and fibrinolysis parameters were measured in 60 type 2 diabetic patients (M:F 1:1) with (n=40) and without (n=20) diabetic microvascular complications and in 30 nondiabetic healthy subjects (M:F 1:1).

Results: The mean age of diabetic patients and healthy controls was 56.9±8.78 and 53.2±7.58 respectively (p=0.05). The plasma levels of PAI-1 (22.6±6.85 vs 44.8±20.8,p=0.00), serum fibrinogen (227.5±22.8 vs 252.75±40.23,p=0.002) and vWF activity (99.4±28.18 vs 144.78±36.21,p=0.00) were found to be increased in diabetics compared to healthy controls. Plasma PAI-1 levels (37.15±15.18 vs 48.65±22.29,p=0.0) and vWF activity (123.19±29.63 vs 155.57±34.61,p=0.007) were significantly increased in diabetic patients with microvascular complications than those without microvascular complications. Amongst the diabetic patients, protein S activity (63.05±16.85 vs 51.59±10.7,p=0.002) was significantly lower in patients with microvascular complications than in patients without these complications.

Diabetic retinopathy was associated with decreased protein S levels (63.05±16.85 vs 48.48±8.72,p=0.005) and vWF activity (123.19±29.63 vs 151.85±29.74,p=0.009). Diabetic nephropathy was associated with increased PAI-1 levels (39.55±13.20 vs 51.69±26.53,p=0.02) and vWF activity (134.99±32.54 vs 157.57±37.37,p=0.007). Diabetic neuropathy did not show any significant relationship with any of the haemostatic variables.

Conclusion: Hypercoagulable state as indicated by decreased fibrinolysis and increased coagulability is responsible as one of the factors for the development of microvascular complications of diabetes mellitus.

Introduction

80% of patients with diabetes mellitus die a thrombotic death. 75% of these deaths are due to cardiovascular complications and remainder due to cerebrovascular events and peripheral vascular complications.

Patients are considered to have a hypercoagulable state if they have laboratory abnormalities associated with increased risk of thrombosis. Many patients with diabetes mellitus fall into this category. Diabetics suffer from accelerated atherosclerosis too. Vascular endothelium, primary defense against thrombosis is abnormal in diabetes, which plays a role in enhanced activation of platelets and clotting factors seen in diabetes. Various mechanisms have been proposed for endothelial dysfunction e.g. AGEs induced activation of endothelial cells and hyperglycaemic pseudohypoxia leading to protein kinase C activation resulting in altered vascular permeability and basement membrane synthesis.

Coagulation activation markers, as indicated by many studies, such as antithrombin thrombin complexes and prothrombin activation fragment 1+2 are elevated in diabetes. Plasma levels of many clotting factors including fibrinogen, factor VII, factor VIII, factor XI, factor XII, kallikrein, and vWF are elevated in diabetes. Conversely, the level of anticoagulant protein C is decreased. The fibrinolytic system, the primary means of removing clots, is relatively sluggish in diabetes due to abnormal clot structure that is more resistant to degradation and an increase in PAI-1 which inhibits tissue plasminogen activator.

This study was designed to assess changes in coagulation, fibrinolytic processes and vascular endothelial cell function parameters in patients with diabetes mellitus and to assess whether any relationship exists among changes in these parameters and development of microvascular complications.

Materials and Methods

60 type 2 diabetics were recruited in the study. This test group was divided into four subgroups – B, C, D and E on the lines of patients with diabetes with no microvascular complications (n=20), patients with diabetic retinopathy (n=14), patients with diabetic nephropathy (n=16) and patients of diabetes with neuropathy (n=10) respectively. 30 age and sex matched healthy subjects without diabetes were put in the control group i.e. group A. Retinopathy was diagnosed on the basis of fundoscopic examination and fluoroscine angiography. Any patient with microalbuminuria or overt proteinuria i.e. albumin test positive in ≥2 consecutive urine samples without urinary infection, cardiac disease or prostate disease were considered to have nephropathy. Microalbuminuria is defined as protein excretion of 30-300 mg/day on at least 2 consecutive occasions. The diagnosis of neuropathy was based on presence of symptoms and signs of neuropathy i.e. any or combination of neuropathic pain, distal sensory loss, motor weakness of isolated cranial nerve palsies, and autonomic symptoms such as orthostatic hypotension, abdominal bloating, constipation, diarrhea, erectile dysfunction.
Table 1 : Clinical and Biological parameters of controls and patients with diabetes

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Controls Gp A</th>
<th>Diabetic Pts. Gp B+C+D+E</th>
<th>P-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>30</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>53.2±7.38</td>
<td>56.9±8.78</td>
<td>0.05</td>
<td>Ns</td>
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<tr>
<td>Sex(F/M)</td>
<td>15/15</td>
<td>30/30</td>
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<tr>
<td>Common Coagulation Studies</td>
<td></td>
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<tr>
<td>Plt. Count</td>
<td>2.4±0.63</td>
<td>2.02±0.61</td>
<td>0.002</td>
<td>S</td>
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<tr>
<td>PT</td>
<td>13.6±0.89</td>
<td>14.01±0.98</td>
<td>0.05</td>
<td>NS</td>
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<tr>
<td>PTT</td>
<td>34.03±0.36</td>
<td>34.6±0.12</td>
<td>0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>227.5±22.8</td>
<td>252.75±40.23</td>
<td>0.002</td>
<td>S</td>
</tr>
</tbody>
</table>

Special Coagulation Studies

| ATIII        | 95.6±16.07   | 95.8±12.17               | 0.95    | NS           |
| PrC          | 96.9±16.4    | 100.0±24.6               | 0.5     | NS           |
| PrS          | 57.9±11.54   | 55.4±14.06               | 0.39    | NS           |
| PAI-I        | 22.2±6.85    | 44.8±20.8                | 0.00    | S            |
| vWF          | 99.4±28.18   | 144.78±36.21             | 0.00    | S            |
| Factor V     | 99.1±2.63    | 98.75±4.07               | 0.7     | NS           |
| Factor VIII  | 98.66±3.83   | 97.7±4.66                | 0.3     | NS           |
| Factor IX    | 100±0.0      | 99.28±2.45               | 0.07    | NS           |

was found to be statistically significant (22.2±6.85 vs 44.8±20.8, p=0.0). vWF levels were increased in diabetics as compared to controls and this difference was found to be statistically significant (99.4±28.18 vs 144.78±36.21, p=0.0).

Significant age difference was observed between diabetic patients without complications and diabetic patients with complications (52.45±8.21 vs 59.12±8.29, p=0.0004) (Table 2). This probably was a reflection of increase in complications with increasing duration of diabetes. Protein S was less in diabetic patients with complications as compared to those without complications and this difference was statistically significant (63.05±16.85 vs 51.59±10.7, p=0.002). PAI-1 and von Willebrand factor activity was raised in diabetic patients with complications compared to those without complications and again the difference was statistically significant (37.15±15.18 vs 48.65±22.29, p=0.04) and 123.19±29.63 vs 155.57±34.61, p=0.007 respectively).

Comparison of patients with and without diabetic retinopathy (Table 3) showed that Protein S was less in diabetic patients with retinopathy as compared to those without complications and this difference was statistically significant (63.05±16.85 vs 51.59±10.7, p=0.002). vWF activity was increased in patients with retinopathy compared to those without this complication (123.19±29.63 vs 155.57±34.61, p=0.007 respectively).

Statistically significant increase in PAI-1 levels (39.55±13.20 vs 51.69±26.53, p=0.02) and vWF activity (134.99±32.54 vs 151.85±29.74, p=0.009) was found in patients with diabetic nephropathy when they were compared with subjects without nephropathy (Table 4).

Results

In comparison between patients with and without diabetes (Table 1), platelet count was found to be decreased in patients with diabetes, but within the normal range and this difference between two groups was found to be statistically significant (2.44±0.63 vs 2.02±0.61, p=0.002). Statistically significant difference was found in serum fibrinogen levels in diabetics and controls (227.5±22.8 vs 252.75±40.23, p=0.002). PAI-1 levels were increased in diabetics as compared to controls and this difference was found to be statistically significant (22.2±6.85 vs 44.8±20.8, p=0.0).

Discussion

Diabetes is associated with increased risk of atherosclerosis, so diabetes is a procoagulant state. To investigate the coagulation abnormalities that leads to hypercoagulability in diabetes was the purpose of this study and whether any relationship, between these hemostatic abnormalities and development of microvascular complications exists or not, was another aim of this study. Very few reports are available regarding coagulation screening tests in diabetes. Acang and Jalil reported shorter PTs.
and aPTTs in diabetics. Conversely, Collier et al found normal PTs in patients with type 2 diabetes. Erem et al reported normal PTs and aPTTs in diabetics. In our study, we did not find any difference in diabetics. Platelet counts have been found to be normal in some studies or decreased in others. Between controls and diabetics, levels of antithrombin III, protein C and S did not differ significantly in our study but Protein S was less in diabetic patients with complications compared to those without complications.

Various investigators have found normal, increased and decreased ATIII, Protein C and S levels in diabetes. Protein C levels were found to be decreased or increased. Between controls and diabetics, levels of antithrombin III, protein C and S did not differ significantly in our study but Protein S was less in diabetic patients with complications compared to those without complications.

We found PAI-1 to be increased in diabetics compared to non-diabetics indicating decreased fibrinolysis in diabetes. This correlates well with various studies which have demonstrated high levels of PAI-1 in diabetes. Protein C levels were found to be decreased or increased. Between controls and diabetics, levels of antithrombin III, protein C and S did not differ significantly in our study but Protein S was less in diabetic patients with complications compared to those without complications.

VIII and von Willebrand factor has been studied by various groups. Factor VIII activity rise in diabetic patients with complications compared to those without complications. vWF activity was found to be increased in diabetics compared to controls. This is in concordance with various other studies and vWF activity was raised in diabetic patients with complications compared to those without complications. vWF has been related to development of nephropathy and neuropathy but not to development of retinopathy. In our study, vWF activity was raised in diabetic patients with retinopathy compared to those without retinopathy. It was also raised in patients with diabetic nephropathy compared to those without nephropathy.

### Conclusion

It has been shown that diabetes is a procoagulant state. This pathophysiology of this procoagulant state is partially understood. Hypercoagulability as evidence by increased fibrinogen levels, decreased protein S levels and increased production of von Willebrand factor by endothelium and hypofibrinolysis as evidenced by increased PAI-1 levels contribute to procoagulant state observed in diabetes. This procoagulant state not only contributes to major vessel diseases
but also contributes to microvascular complications as has been observed in this study.

References


