Turkish Journal of Endocrinology and Metabolism, (1999) 1 : 1-4 **ORIGINAL ARTICLE**

The Effect of Glycaemic Control on Fibrinolytic Parameters in Diabetic Patients with or without Background Retinopathy

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The contribution of fibrinolytic system abnormalities to the development of diabetic micro- and macrovascular complications is still controversial. However, most studies indicate that diabetes is associated with hypofibrinolysis and increased coagulation. In this study, we aimed to investigate; 1) whether there is a difference in plasma antigen levels of plasminogen, tissue plasminogen activator-plasminogen activator inhibitor-1 complex (t-PA-PAI-1 complex) and D-Dimer between poorly-controlled diabetic patients and healthy controls; 2) a possible effect of good glycaemic control on these parameters; 3) a possible relationship between diabetic retinopathy and these parameters. Twenty-eight poorly-controlled diabetic patients with and without diabetic background retinopathy were included in the study. The control group consisted of 23 age-, sex-, and body mass index-matched healthy subjects. After three months, good glycaemic control (HbA1c < 8 %) was achieved in 17 patients. Six patients remained in poor glycaemic control. Functional activity of plasminogen was measured by a colorimetric method. Plasma antigenic levels of t-PA-PAI-1 complex and D-Dimer were measured by EIA. Functional activity of plasminogen in poorly-controlled diabetic patients (baseline) was higher than that of healthy subjects. Plasma antigenic levels of t-PA-PAI-1 complex and D-Dimer were comparable in poorly-controlled diabetic patients and healthy subjects. Good glycaemic control didnot have any significant effect on plasma levels of plasminogen, t-PA-PAI-1 complex and D-Dimer. There was no significant difference in the same parameters between patients with and without diabetic background retinopathy. In conclusion, our study suggests that the fibrinolytic pathway is not inhibited in diabetic patients. A short term good glycaemic control does not affect the fibrinolytic parameters, and fibrinolytic pathway abnormalities are not responsible in the pathogenesis of background diabetic retinopathy.

KEY WORDS Diabetes mellitus, glycaemic control, fibrinolytic parameters, background retinop athy

Introduction

The contribution of fibrinolytic system abnormalities to the development of diabetic micro- and macrovascular complications is still controversial (1-3). Activity of the fibrinolytic system in diabetic patients was found to be increased (4-10), decreased (11-14) or unchanged (15) in several studies. However, most studies indicate hypofibrinolysis leading to increased coagulation. Hypofibrinolysis may occur due to reduced expression of tissue plasminogen activator (t-PA) (16), which is the most important activator of plasminogen, or increased plasminogen activator inhibitor-1 (PAI-1) (17-19), which binds to t-PA and forms t-PA-

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PAI-1 complex (which reflects induction of fibrinolytic pathway).

It is well known that good glycaemic control delays the occurrence and progression of microvascular complications (20-21). However, the effect of good glycaemic control on fibrinolytic pathway is still controversial.

In this study, we aimed to investigate;

1. Whether there is a difference in plasma antigen levels of plasminogen, t-PA-PAI-1 complex and D-Dimer (which is an end product of fibrin and reflects reactive fibrinolysis and coagulation activation) between poorly-controlled diabetic patients and healthy controls,
2. A possible effect of good glycaemic control on these parameters,
3. A possible relationship between diabetic retinopathy and these parameters.

Patients and Methods

Twenty-eight poorly-controlled diabetic patients [with diabetic background retinopathy (n=12), without retinopathy n=16)] were included in the study (Table 1).

Table 1. Characteristics of diabetic patients and healthy controls. Data are given as median (range).

	diabetic patients	healthy controls	p
N	28	23	
Sex (M/F)	13/15	13/10	
Age (years)	56(29-68)	50(27-65)	> 0.05
BMI (kg/m^2)	26.3(16.9-33.5)	25.7(20.8-31.2)	> 0.05
Duration of diabetes (years)	5.5(0-26)	-	
IDDM/NIDDM	2/26	-	
HbA1c (%)	11.8(8.4-19)	5.3(4.9-7.2)	< 0.0001

The patients didnot suffer from major cardiovascular, hepatic and renal disease or malignancy; didnot have a history of thromboembolism and had not taken any drug that could affect haemostatic parameters. Four patients were on diet only, 4 on insulin, and 20 on oral antidiabetics. The control group consisted of 23 age-, sex-, and body mass index (BMI)-matched 23 healthy subjects with no family history of diabetes.

Baseline blood samples were obtained from diabetic patients who had poor glycaemic control. Then, therapeutic regimens of the patients were reviewed and diet, physical activity, oral antidiabetics or insulin doses were adjusted according to weekly fasting and postprandial 2 hours blood glucose levels. After three months, good glycaemic control (HbA1c < %8) was achieved in 17 patients; whereas 6 patients remained in poor glycaemic control (HbA1c > %8). Five patients dropped out of the study because of poor compliance. Blood samples were obtained from patients with good glycaemic control.

Fundoscopic examination of the patients was done by an ophthalmologist.

Blood collection-

Blood samples were obtained with a 19 gauge needle without using a tourniquet and were drawn into plastic tubes containing 3.8 % sodium citrate. The tubes were immediately placed in an ice bath and centrifuged at 2500 g at 4°C for 15 minutes. The supernatant platelet poor plasma was stored at -80°C until assay.

Methods-

Functional activity of plasminogen was measured by a colorimetric method (Stachrom PLG, Diagnostica Stago, Asnieres, France); plasma antigenic levels of t-PA-PAI-1 complex and D-Dimer were measured by EIA (Asserachrom t-PA-PAI-1 and Asserachrom D-Di, Diagnostica Stago, Asnieres, France, respectively). HbA1c was measured by an ion-exchange microcolumn method (Eagle Diagnostics, DeSoto, Texas, USA).

Statistical Analysis-

Mann-Whitney U test was used for comparison of the groups. Wilcoxon Signed-Rank test was used for comparison of results of patients with poor and good glycaemic control. A p value < 0.05 was considered to be statistically significant. All values were given as median (range).

Results

Functional activity of plasminogen in poorly-controlled diabetic patients (baseline) was higher than in healthy subjects (Table 2). There was no significant difference in plasma antigenic levels of t-PA-PAI-1 complex and D-Dimer between poorly-controlled diabetic patients and healthy subjects. Good glycaemic control didnot have any significant effect on plasma levels of plasminogen, t-PA-PAI-1 complex and D-Dimer (Table 3).

The same parameters were comparable in patients with diabetic background retinopathy and without retinopathy (Table 4).

Table 2. Plasma levels of fibrinolytic parameters in diabetic patients (n=28) and healthy subjects (n=23). Data are given as median (range).

	diabetics with poor control	healthy controls	p
Plasminogen (%)	97(71-127)	91(77-111)	0.04
t-PA-PAI-1 complex (%)	8(0-170)	6(0-86)	> 0.05
D-Dimer (ng/mL)	348(130-1509)	302(122-808)	> 0.05

Table 3. The effect of good glycaemic control on fibrinolytic parameters (n=17). Data are given as median (range).

	baseline	after 3 months	p
Plasminogen(%)	97(71-127)	94(74-116)	> 0.05
t-PA-PAI-1 complex (%)	8(0-170)	12(0-240)	> 0.05
D-Dimer (ng/mL)	288(183-721)	313(163-1231)	> 0.05
HbA1c (%)	11.6(8.4-19)	6.6(5.2-7.8)	< 0.0001

Table 4. The comparison of fibrinolytic parameters between patients with background retinopathy and without retinopathy. Data are given as median (range).

	with background retinopathy (n=16)	without retinopathy (n=12)	p
Plasminogen(%)	97(71-127)	99(85-108)	> 0.05
t-PA-PAI-1 complex (%)	2(0-170)	11(0-104)	> 0.05
D-Dimer (ng/mL)	396(216-1180)	261.5(130-1509)	> 0.05
HbA1c (%)	11.8(8.4-15.7)	11.4(8.6-19)	> 0.05

Discussion

The finding of a higher functional activity of plasminogen in poorly-controlled diabetics than in healthy controls may be interpreted as less fibrinolytic pathway inhibition in poorly-controlled diabetics. This may reflect activation of fibrinolytic pathway due to microthrombosis caused by chronic, increased procoagulant activity in diabetes (22).

However, there are some studies which suggest that the hyperglycaemic milieu in poorly controlled diabetic patients reduces the functional activity of plasminogen via nonenzymatic glycosylation (6). Our findings do not support this hypothesis and are in contrast with the general literature data. In our patients, accomplishment of good glycaemic control with in 3 months had no effect on functional plasminogen activity. This discrepancy may be due to the heterogenity of the patients with respect to sex, age, race, smoking etc.

We didnot find any difference in antigenic levels of t-PA-PAI-1 complex and D-Dimer between diabetics and controls. This finding is consistent with normal fibrinolytic pathway in diabetes.

There was no association between diabetic retinopathy and fibrinolytic parameters. This suggests that fibrinolytic abnormality is not responsible at least in the pathogenesis of background diabetic retinopathy.

In contrast to our findings, increased activity of fibrinolysis in early diabetic retinopathy and decreased activity in the proliferative period of retinopathy have been reported in the literature (14).

In conclusion, our study suggests that fibrinolytic pathway is not inhibited in diabetic patients. Furthermore, a short term (3 months) good glycaemic control doesnot affect the fibrinolytic parameters,and fibrinolytic pathway abnormalities are not responsible in the pathogenesis of background diabetic retinopathy.

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