

ORIGINAL ARTICLE

Fibrinolytic activity in Nigerian diabetics

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Fibrinolytic activity, using euglobulin lysis time (ELT), was assessed in 46 Nigerians with type 2 diabetes mellitus to study the effect of the disease on fibrinolytic component of haemostasis. There were 20 females and 26 males. Fifty age matched non-diabetics and apparently healthy Nigerians were similarly studied as controls; there were 24 females and 26 males. In the patients, the mean (SD) age of the females was 56.7 (12.0) years and mean (SD) ELT was 276.4 (62.2) min; the mean age of the males was 55.7 (8.5) years and mean ELT was 303.5 (51.5) min. The mean age for female controls was 54.3 (12.6) years and their mean ELT was 198.3 (37.5) min; the mean age of the male controls was 53.4 (11.0) years and mean ELT was 181.6 (39.4) min. There was reduced fibrinolytic activity in diabetic Nigerians as revealed by significantly prolonged ELT in diabetic patients compared with healthy controls. There was good correlation between the blood glucose level and ELT. The observed changes in fibrinolytic activity in this study were not affected by duration of illness. The prolonged ELT in the diabetic population is an additional risk factor for thromboembolic disorders. Fibrinolytic agents may therefore be useful in the management of diabetes mellitus.

Diabetes mellitus is a complex metabolic derangement characterised by either relative or absolute insulin deficiency that results in disturbance of carbohydrate metabolism leading to excessive glucose in the blood, excretion of glucose in the urine, incomplete oxidation of fats, and attending symptoms of thirst, polyuria, and wasting.^{1,2} The morbidity and mortality associated with diabetes mellitus results from either acute or chronic complications. Chronic complications are known to give rise to microvascular disorder such as retinopathy, nephropathy, and neuropathy. Other chronic complications include macrovascular disorders such as atherosclerosis.³ Atherosclerosis is a recognised major cause of mortality in the diabetic population,^{3,4} and it is implicated in the circulatory disturbances seen in diabetes.^{4,5} The circulatory disturbances are further compounded by alteration in platelet count and activity, coagulopathy, fibrinolytic aberration, changes in endothelial metabolism, and haemorrhological factors.^{4,6} Many of the previous studies on haemostatic changes in diabetic Nigerians focused on platelet count and activity⁶ with scanty information on coagulation profile and fibrinolytic activity. Furthermore, racial factors have been shown to influence fibrinolytic activity: contrary to published findings,⁸ high tissue type plasminogen activators activity and a good fibrinolytic response without significant changes in plasminogen activator inhibitor type I activity was found in Chinese patients with diabetes.⁷ For these reasons, it was important to study fibrinolytic activity in a population of diabetic Nigerians.

METHODS

Consecutive normotensive Nigerians with type 2 diabetes mellitus attending the diabetes clinic of Obafemi Awolowo University Teaching Hospitals' Complex, Ile-Ife (in the south west of Nigeria) were prospectively studied for euglobulin lysis time (ELT) after ethical clearance from the hospital and the patients had given informed consent. The patients were diagnosed and classified according to World Health Organisation and the American Diabetes Association criteria.⁹ To determine the ELT, 9 ml of venous blood was collected after a resting period of at least 30 minutes, under aseptic technique and without stasis, from each of the patients and

50 age matched apparently healthy Nigerians who were similarly studied. This was added to 1 ml of sodium citrate (31.3 g/l). The sample was spun at 2500 rotations/min for 10 minutes to separate plasma. The supernatant obtained was kept at 4°C until the test for fibrinolytic activity, using the ELT method as described by Von Kaulla,¹⁰ was performed in duplicate on each sample. In all cases, tests were performed within 12 hours of sample collection and values obtained were recorded in minutes. The latest fasting blood glucose result as at the time of the study (using the glucose oxidase/peroxidase method) was recorded for each patient. Other clinical parameters such as sex, age, weight in kg, and duration of diabetes were also noted and recorded. The type of treatment offered each patient was also noted. Random blood glucose, using a glucometer with appropriate glucose strips, was determined in the controls (made up of volunteers from hospital workers, prospective blood donors, and surgical patients awaiting herniorrhaphy) to exclude those with hyperglycaemia. The values obtained were all subjected to statistical analysis. Corresponding values were compared in pairs using independent samples *t* test (Statistical Package for Social Sciences 10.0 (SPSS) software).

RESULTS

Forty six patients were studied. Their ages ranged from 40 years to 88 years. Two patients (4%) were taking oral hypoglycaemic agents and insulin for their glycaemic control while the remaining 44 (96%) patients were on combination therapy of oral hypoglycaemic agents (sulphonurea and biguanides). The mean (SD) age and sex distribution are shown in table 1. Their mean (SD) weight was 70.6 (8.2) kg. Identified by sex, the mean weight of the female patients was 72.1 (10.7) kg while that of the males was 69.6 (10.4). The mean fasting blood glucose and mean ELT were 9.4 (3.9) mmol/l and 291.0 (57.4) min respectively. The mean ELTs by sex and duration of illness are shown in tables 1 and 2.

Fifty age matched controls (mean age 53.8 (11.7) years and mean weight 72.5 (7.1) kg) were similarly studied and had their results tabulated as for the patients for comparison (tables 1 and 2).

There was a statistical difference between the mean ELT of the control subjects and that of the patients ($p = 0.0001$), but

Table 1 Comparison of mean (SD) age and ETL time in categories of patients and controls by sex

Parameters studied	Female patients (n = 20)	Male patients (n = 26)	p Value	Female controls (n = 24)	Male controls (n = 26)	p Value
Age (years)	56.7 (12.0)	55.7 (8.5)	0.77	54.3 (12.6)	53.4 (11.0)	0.80
ELT (min)	276.4 (62.2)	303.5 (51.5)	0.12	198.3 (37.5)	181.6 (39.4)	0.13

there was no statistical difference between the ELT values of the female and male patients ($p = 0.12$), just as there was no statistical difference between the mean ELT values for female and male controls ($p = 0.13$) (table 2). There was good correlation between the blood glucose concentration and mean ELT (Pearson's correlation = 0.81).

When subgrouped according to the duration of illness, patients with illness of less than one year had a mean ELT of 297.5 (44.0) and those with illness of more than one year had an ELT of 287.4 (66.4) min. There was no statistical difference between the two values ($p = 0.54$; table 2).

DISCUSSION

In consecutive selection of normotensive Nigerians with type 2 diabetes mellitus attending our diabetes clinic, 20 female and 26 male patients were recruited. The population studied tends to suggest that there is an absence of gender predilection, confirming an earlier study in Africans with diabetes.¹¹ However, a larger series of patients would be necessary to ascertain this.

The mean weight of the patients studied did not reflect the characteristic obesity associated with type 2 diabetes.⁸ This could be a reflection of race and/or the general nutritional status of Africans as suggested by the comparable mean weights of the patients and the controls. However, body mass index, which was not studied in our patients, could be more informative.

Although the original technique for determining fibrinolytic activity using ELT¹⁰ has been variously modified, including the introduction of a microplate reader,¹²⁻¹³ because of our limited facilities we had to use the original method without modification in both the patients and controls. This, we believe, does not invalidate comparison of our results with those from resource-rich centres.

There have been conflicting reports on the mean ELT in males compared with that of females. Many reports have shown no difference in ELT values for both sexes,¹⁴⁻¹⁶ while several others have suggested higher values in males than females¹⁷⁻¹⁸ or higher values in females than males.¹⁹ In this study, there was no significant difference between the ELT values in males and females both in health and disease

(table 2). This finding lends credence to the theory of equal fibrinolytic activity in both males and females, given the same state of health. It also suggests that sex hormones have no significant effect on fibrinolytic activity.

There was significant prolongation of mean ELT in patients compared with that of controls (table 2). A similar finding had been documented and related to glycaemic control using the level of glycated haemoglobin (HbA1c).²⁰ The prolonged ELT in diabetes has been attributed to the increased levels of plasminogen activator inhibitor type I and lipoprotein (LPA) found.²¹⁻²² This study also showed good correlation between the blood glucose level and ELT. Even though the mean fasting glucose level used in this study may not be as sensitive as glycated haemoglobin²⁰ or red cell sorbitol concentrations²³⁻²⁴ in the assessment of metabolic control in diabetes, our findings agreed with those of other workers outside Africa.²⁵⁻²⁶ Another factor shown to decrease the cardiovascular events associated with fibrinolysis is the oral hypoglycaemic agent metformin.²⁷⁻²⁸ Despite being on oral hypoglycaemic agents, including metformin, our patients still had prolonged ELT, indicating poor fibrinolytic activity. This may be because of the complex independent contribution of other risk factors associated with impaired fibrinolysis.²⁹

Furthermore, duration of illness did not affect ELT in our patients (table 2) as there was no significant difference in the ELT values of patients with less than one year's illness and those with more than one year. This is in keeping with an earlier study with similar finding²¹ and supports the submission that although hypercoagulability in diabetes could be related to poor glycaemic control, haemostatic disturbances could not be secondary to metabolic disorders caused by the disease but to subclinical alterations of demonstrable vascular complications.²⁰⁻³⁰ ELT would, therefore, not be a good test in monitoring the course of the disease in diabetes but would be invaluable in predicting vascular abnormalities associated with diabetes and therefore enhances early diagnosis, especially in older patients with type 2 diabetes.

In conclusion, the findings in this study demonstrate decreased fibrinolytic activity in diabetes mellitus irrespective of age, sex, duration of illness, and blood glucose control. It therefore confirms diabetes as predisposing to thrombosis. Early use of antithrombotic agents, especially antifibrinolytic agents, is therefore suggested in Nigerian diabetics.

Table 2 Statistical comparison of ELT in paired groups of patients and controls

Paired group	Mean (SD) ELT (min)	p Value
Type II diabetes	291.7 (57.4)	0.01*
Controls	189.6 (39.1)	
Duration of illness		0.54
<1 year	297.5 (44.0)	
>1 year	287.4 (66.4)	
Controls		0.13
Female (n = 24)	198.3 (37.5)	
Males (n = 26)	181.6 (39.4)	0.12
Patients		
Females (n = 20)	276.4 (62.2)	
Males (n = 26)	303.5 (51.5)	

*Significant.

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