African Journal of Biotechnology Vol. 7 (10), pp. 1400-1403, 16 May, 2008
Available online at http://www.academicjournals.org/AJB
ISSN 1684–5315 © 2008 Academic Journals

Full Length Research Paper

Haemorrheologic and fibrinolytic activities in diabetics resident in Calabar, Cross-River State, Nigeria

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Accepted 7 April, 2008

Diabetes mellitus is a major health problem that results in significant morbidity and mortality from such complications as neuropathy, peripheral vascular disease and macrovascular disease. Many of the previous haemostatic studies in diabetic Nigerians focused on platelet count and activity with scanty information on haemorrheologic and fibrinolytic activities. A total of 50 diabetic subjects aged between 35 - 75 years attending the diabetic clinic of University of Calabar Teaching Hospital were selected for the study. 50 age-matched non-diabetic apparently healthy volunteers were used as controls. Fasting blood sugar (FBS), relative plasma viscosity (RPV), plasma fibrinogen concentration (PFC) and euglobulin lysis times (ELT) were estimated using standard methods. There was significant increase in FBS, RPV, PFC and ELT of diabetics when compared with the non-diabetic controls ($P < 0.05$). The duration of diabetes (< 5 years vs. ≥ 5 years) did not show any statistically significant effect on RPV, PFC and ELT ($p > 0.05$). It was observed in this study that the diabetic subjects had defective fibrinolysis and hyperviscous plasma as revealed by significantly increased RPV, PFC and prolonged ELT when compared with apparently healthy controls. This shows that the diabetics are prone to developing vascular and thrombotic complications. It may be necessary to incorporate RPV, PFC and ELT as routine tests for better management of these patients.

Key words: Haemorrheologic, fibrinolytic, diabetes mellitus, thrombosis.

INTRODUCTION

Diabetes mellitus, a syndrome characterized by chronic hyperglycemia due to absolute or relative deficiency of insulin is estimated to afflict over 170 million people world wide and this represents about 2% of the world's population (Wokoma, 2002). In Nigeria, about 1-7% of the population is affected, with over 90% of these being non-insulin dependent (Fabiyi et al., 2002). The prevalence rate among students of University of Calabar was 0 - 4% (Anwan et al., 1998). The long-term effects of diabetes include progressive development of the specific complication of retinopathy, nephropathy, and neuropathy with microvascular and macrovascular diseases (McFarlane, 1997). Macrovascular disorders such as atherosclerosis, is a recognized major cause of mortality in the diabetic population, and it is implicated in the circulatory disturbances seen in diabetes. The circulatory disturbances are further compounded by alteration in platelet count and activity, coagulopathy, fibrinolytic aberration, haemorrheological factors and changes in endothelial metabolism (McFarlane, 1997). This investigation of hacmorrheologic activity on diabetics was triggered by the work of Oviasu et al. (1998), who reported that increased plasma viscosity in nephrotic patients could on the long term predispose them to increased risk of cardiovascular morbidity. Also, Aigbe and Famodu (1999), in their work on the haemorrheologic and fibrinolytic activity in hypertensive Nigerians, reported that a defective rheology and fibrin-clearing mechanisms may contribute to the aetiology of vascular complication in hypertensive patients especially on the long term.

Many of the previous studies on haemostatic changes in diabetic Nigerians focused on platelet count and activity with scanty information on coagulation profile and fibrinolytic activity. For these reason, it was important to study fibrinolytic activities in a population of Nigerian

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Table 1. Fasting blood sugar (FBS), relative plasma viscosity (RPV), plasma fibrinogen concentration (PFC), and euglobulin lysis time (ELT) in diabetic and non-diabetic subjects.

Subjects	FBS (mmol/L)	RPV	PFC (g/L)	ELT (min)
Diabetics (n = 50)	10.23±4.85	1.65±0.08	5.22±1.89	268.4±56.9
Non-diabetics (n = 50)	3.86±0.35	1.49± 0.06	2.50±0.65	147.6±46.96
P value	<0.05	<0.05	<0.05	<0.05

Table 2. Relative plasma viscosity, plasma fibrinogen concentration and euglobulin lysis time based on age.

Age range (years)	RPV	PFC (g/L)	ELT (min)
Diabetics 35- 55years (n=25)	1.67±0.07	5.2±1.76	259.0±58.6
56 – 75 years (n = 25)	1.64±0.08	5.31±2.0	277.8±54.9
P value	>0.05	>0.05	>0.05
Non-Diabetics 35 – 55 years (n = 44)	1.50±0.05	2.50±0.63	149.20±48.30
56 – 75 years (n = 6)	1.51±0.09	2.54±0.84	135.83±37.34
P value	>0.05	>0.05	>0.05

diabetics. This study was aimed at determining the plasma viscosity, euglobulin lysis time, and fibrinogen levels in diabetics.

MATERIALS AND METHOD

A total of 50 diabetic subjects (both males and females) aged between 35 - 75 years attending the diabetic clinic of University of Calabar Teaching Hospital, were selected for the study. Diabetes in this study was defined based on laboratory findings as a fasting plasma glucose levels greater than 7.0 mmol/L in two or more occasions (WHO, 1999). Their medical history and personal data were obtained via a comprehensive questionnaire and from their case notes after due approval from the ethical committee of the hospital.

Fifty age-matched non-diabetic apparently healthy volunteers (both males and females) living in Calabar municipality were used as controls in this study. They were selected from blood donors, staff of UCTH, and workers of Calabar municipal council. Informed consent was obtained from all the participants.

Seven millitres (7 ml) of venous blood was collected from each subject and 4.5 ml was added to 0.5 ml of sodium citrate anticoagulant (31.3 g/L) for coagulation studies while 2 ml was dispensed into fluoride oxalate bottle for the determination of fasting blood sugar. For the coagulation studies, the whole blood was spun at 3000 rpm for 10 min to obtain platelet poor plasma required for the analysis. Tests were performed within 3 h of sample collection and in duplicates. Standard methods of Haugie (1986), Reid and Ugwu (1987) Ingram's and Hills (1976) and Nelson (1944) were employed for the determination of euglobulin lysis time, relative plasma viscosity, plasma fibrinogen concentration and fasting blood sugar levels, respectively.

RESULTS

This study examined haemorrheologic and fibrinolytic activities in diabetics resident in Calabar municipality. The tests that were carried out include the determination of relative plasma viscosity (RPV), plasma fibrinogen concentration (PFC) and the euglobulin lysis time (ELT). Fasting blood sugar (FBS) levels were also determined using standard biochemical procedures. Table 1 shows the means of the various parameters analysed. The mean fasting blood sugar, relative plasma viscosity, plasma fibrinogen concentration and euglobulin lysis time of diabetic patients were significantly ($P<0.05$) higher than that of the control subjects. The mean relative plasma viscosity, plasma fibrinogen concentration and euglobulin lysis time in both diabetics and non-diabetics subjects based on age is shown in Table 2. In the age range 35 - 55 years, the mean values obtained showed no significant difference ($p>0.05$) when compared with the age range of 56 - 75 years for both the diabetics and control subjects.

The haemorrheologic and fibrinolytic activities based on gender of diabetics and non-diabetic subjects is shown in Table 3. In both the diabetic and control groups, there was no significant difference ($P>0.05$) in the mean values obtained for relative plasma viscosity, plasma fibrinogen concentration and euglobulin lysis time. The diabetic subjects were divided into two groups: those with less than five years duration and those with five or more year's duration and the haemorrheologic and fibrinolytic activities compared (Table 4). The mean relative plasma viscosity, plasma fibrinogen concentration and euglobulin lysis times of those diabetics less than 5 years duration did not significantly ($P>0.05$) differ when compared with those for 5 years and more duration.

DISCUSSION

Diabetes mellitus is a syndrome characterized by presence of chronic hyperglycaemia due to defective insulin secretion, insulin action or both. It is estimated to afflict over 170 million people worldwide (Wokoma, 2002). The

Table 3. Haemorrheologic and fibrinolytic activities of diabetic and non-diabetic subjects based on gender.

Gender	RPV	Fibrinogen (g/L)	ELT (min)
Diabetic males (n = 20)	1.66±0.07	5.1±1.80	274.0±59.55
Diabetic females (n = 30)	1.64±0.08	5.3±1.97	264.67±55.93
P value	>0.05	>0.05	>0.05
Non-diabetic males (n = 30)	1.49±0.05	2.33±0.66	136.5±37.67
Non-diabetic females (n = 20)	1.50±0.07	2.75±0.55	164.25±55.09
P value	>0.05	>0.05	>0.05

Table 4. Haemorrheologic and fibrinolytic activities in diabetic subjects based on duration of disease.

Duration (years)	RPV	PFC (g/L)	ELT (min)
<5 (n = 42)	1.64±0.08	5.05±1.94	268.33±56.84
≥ 5 (n = 8)	1.70±0.07	6.13±1.33	268.75±70.39
P value	>0.05	>0.05	>0.05

long term effects of diabetes which include progressive development of the specific complication of retinopathoy, nephropathy, neuropathy with microvascular disorders such as atherosclerosis, are recognized major cause of mortality in the diabetic population, and it is implicated in the circulatory disturbances seen in diabetes (Wokoma, 2002). The circulatory disturbances are further compounded by alteration in platelet count and activity, coagulopathy, fibrinolytic aberration, haemorrheologic factors and changes in endothelial metabolism (Omar and Ayesha, 2002).

It was observed in this study that, the diabetic subjects had defective fibrinolysis and hyperviscous plasma as revealed by significantly increased RPV (1.65 ± 0.08), PFC (5.22 ± 1.89 g/l), and prolonged ELT (268.4 ± 56.9 min) when compared with apparently healthy controls who had 1.49 ± 0.06, 2.50 ± 0.65 g/l, and 147.60 ± 46.96 min, respectively. This raised plasma viscosity causes sluggish flow in microcirculation and results in insufficient tissue perfusion (Grigoleit et al*.,* 1973). The elevated RPV is apparently due to the observed high concentration of fibrinogen (Mcmillan, 1983). The implication of this finding is that the observed increase in RPV could predispose diabetics to high risk for peripheral arterial and heart disease and peripheral resistance thus promoting elevation of blood pressure. The findings agree with previous investigations of Baker (1991) and Aigbe and Famodu (1999). The resulting phenomenom coupled with abnormal fibrinolysis increases stasis and lead to hypercoagulability state. When age and gender were considered, there was no statistical difference in RPV (P>0.05) for both diabetic subjects and the controls. This agrees with the fact that measurement of plasma viscosity is a useful screening test for detecting alterations in plasma proteins in acute and chronic diseases (Leonhardt et al., 1977), and has the considerable advantages of being unaffected by the age and gender of the patient (Mohandas et al*.,* 1979).

This study observed that RPV of diabetics with less than five years duration (1.64 ± 0.08) showed no significant difference when compared with those who had diabetes for five or more years (1.70 ± 0.07). Fibrinogen levels in diabetics were significantly higher (P<0.05) when compared with the control subjects. This agrees with a similar study by Tkac et al. (2001), who reported significantly higher levels of fibrinogen in diabetics. The hyperfibrinogenemia in diabetics has been reported to be due to increased synthesis of fibrinogen that is not compensated for by a proportional increase in fibrinogen clearance (Defeo et al., 1996). These abnormalities are associated with insulin deficiency which Defeo et al*.* (1996) reported was corrected with insulin, suggesting that hyperfibrinogenaemia is an expression of poor glycaemic control. In diabetic patients, the blood viscosity is increased which favours the process of thrombosis. This is attributed to increased plasma fibrinogen levels which predispose them to ischemic heart disease through different pathways, mainly the development of atherosclerotic plaque, platelet aggregation and as a substrate in coagulation scheme (Brunner et al., 1996). There was no significant difference in fibrinogen level when age and gender were considered.

The ELT of diabetics (268.4 ± 56.9 min) was observed to be significantly higher than that of the control subjects (147.6 ± 46.96 min). The prolonged ELT in diabetes has been attributed to the increased levels of plasminogen activator inhibitor Type I and lipoprotein (Adediren et al*.,* 2004). Previous studies have shown that there was extensive alteration of inhibitor to plasmingen activator in diabetes (Makris et al*.,* 1997). Perhaps, the increase in fibrinolytic inhibitor could be responsible for the prolonged lysis time observed in the study. Earlier observation on

abnormal fibrinolytic activities in diabetics has been reported (Scheinman, 1991). Recently, hypoalbuminaemia itself has been identified as a possible factor causing impaired fibrinolysis, with the suggestion that albumin is a co-factor for the binding of plasminogen to fibrin and the subsequent interaction with tissue plasminogen activator (Gandrille, 1990). There was no significant difference in ELT when age and sex were considered. 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. Furthermore, duration of illness did not affect ELT in the diabetics, as there was no significant difference in ELT values of subjects with less than 5 years duration and those with five or more years. This 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 (Adediran et al., 2004). 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 (Vinik et al., 2001). The observation in this study agrees with that of Adediran et al. (2004) who reported that duration of diabetes did not affect ELT in their subjects.

This study has established base line values of RPV, PFC and ELT in diabetics and control subjects in this locality. It has also shown that there is a significant increase in haemorrheology and reduced fibrinolytic activities in diabetic subjects. In conclusion, the study observed defective rheology and fibrin clearing in diabetes and this may contribute to the vascular and thrombotic complications usually observed in diabetic subjects. For better management of diabetic patients, it may be necessary to incorporate RPV, PFC and ELT as routine tests.

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