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Full Length Research Paper

Changes in haemorrheologic and fibrinolytic activities upon hypertension and diabetic chemotherapy in Calabar diabetic residents, Nigeria

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This research was carried out to assess the effect of hypertension on haemorrheologic and fibrinolytic activities in fifty (50) diabetics resident in Calabar municipality and the values obtained were compared with those of fifty (50) age and sex-matched non diabetics in the same locality. Relative plasma viscosity plasma fibrinogen concentration, euglobulin lysis time and fasting blood sugar were determined using standard methods. The relative plasma viscosity, plasma fibrinogen concentration, euglobulin lysis time and the fasting blood sugar values were significantly higher in diabetics (P < 0.05) when compared with the controls. Correlation between RPV and duration of diabetes was positive and significant (r = 0.323, p < 0.05). Also, correlation between fasting blood sugar and plasma fibrinogen concentration was positive and significant (r = 0.635, p < 0.05).There was no significant increase in RPV, PFC and ELT of type I diabetes when compared with type II diabetes (P > 0.05). The RPV and ELT of diabetics with hypertension was increased, but showed no significant difference (P > 0.05) with that of those who had no hypertension. However, the PFC of diabetics with hypertension was significantly increased (P < 0.05) when compared with that of the control group. The diabetics who were on oral hypoglycaemic agents and insulin showed no significant difference (P > 0.05) in RPV, PFC and ELT when compared with those who were on combination therapy of oral hypoglycaemic agents (glanil, glucophage), but there was significant increase when RPV, PFC and ELT values were compared with the controls (P < 0.05). This work shows that defective rheology and poor fibrin clearing may be the contributory factor to vascular and thrombotic complications seen in diabetics.

Key words: Hypertension, haemorrheologic, fibrinolytic, diabetes mellitus.

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 (Wokoma, 2002) and this represents about 2% of the world's population. In Nigeria, about 1 - 7% of the population is affected, with over 90% of these being non-insulin dependent (Fabiyi et al., 2002). Diabetes has been classified based on the clinical staging and etiology into type I and type II. Type I or insulin dependent diabetes mellitus (IDDM) or juvenile on-set diabetes is characterized by beta cell destruction leading to absolute insulin deficiency, which may be due to auto-immune mechanism and patients are prone to ketoacidosis (WHO, 1999). Type II or non-insulin dependent diabetes mellitus (NDDM) or adult onset diabetes is predominated by insulin resistance with relative insulin deficiency or an insulin secretary defect. Here, ketoacidosis is infrequent and obesity is a predisposing factor (WHO, 1999).

Most adverse diabetes outcomes are a result of vascular complications both at macro vascular and micro vascular levels (Hogan et al., 2003). Macro vascular complications are more common and up to 80% of patients with type II diabetes will develop or die of macrovascular disease (Evans et al., 2002). Atherosclerosis an example of macro vascular disorder has been recognized as a major cause of mortality in diabetic population (Benett, 1999) and also implicated in the

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

Subjects	FBS (mg/100 ml)	RPV	PFC (g/l)	ELT (min)
Diabetics (n = 50)	184.14± 87.30	1.65 ± 0.08	5.22 ± 1.89	268.4 + 56.9
Non-diabetics (n = 50)	69.48± 6.30	1.49 + 0.06	2.50 + 0.65	147.6 + 46.96
P value	< 0.05	< 0.05	< 0.05	< 0.05

circulatory disturbances seen in diabetics (Colwell et al., 1992).

Plasma viscosity in nephrotic patients and haemorrheologic and fibrinolytic activity in hypertensive Nigerians have been studied (Oviasu et al., 1998, Aigbe and Famodu, 1999). Again reports on alteration in platelet count and activity, coagulopathy and fibrinolytic aberration in diabetic subjects have also been made (Colwell et al., 1992; Adediran et al., 2004) with scanty information on haemostatic changes in diabetic Nigerians particularly those who are on chemotherapy as well as those with hypertension. The increasing prevalence of diabetes and the associated financial burden on our nation's economy is a major challenge for the health sector. Therefore preventive measures may be as important as measures towards discovering a permanent cure for the disease. This work is aimed at determining the plasma viscosity, euglobulin lysis time, and fibrinogen levels in diabetics on chemotherapy as well as those with hypertension and comparing them with non-diabetics who are nomotensive residents in Calabar Municipality. It is believed that this will aid in a better understanding of the haemorrheology of diabetic patients.

MATERIALS AND METHODS

A total of fifty (50) diabetic subjects were included in this study. They were 20 males and 30 females aged between 35 - 75 years attending the diabetic clinic of University of Calabar Teaching Hospital. Of these, 11 (6 females and 5 males) diabetics were with hypertension, while 39 (24 females and 15 males) were without hypertension. Three (3) subjects were on monotherapy (insulin) while the remaining 47 subjects were either on insulin and oral hypoglycaemic agents or a combination therapy of oral hypoglycaemic agents (glanil, glucophage). Diabetes in this study had a fasting plasma glucose levels greater than 126 mg/100 ml in two or more occasions (WHO, 1999). As at the time of study, there were no signs of coexisting disease capable of explaining the abnormally high concentration of glucose as observed from their hospital folders (medical history) and their personal data obtained via a comprehensive questionnaire after due approval from the ethical committee of the hospital. The subjects had diabetes mellitus for an average of 1 – 7 years. Hypertension in this study was defined as a diastolic pressure of 90 mmHg or above, measured while the subject was sitting. The mean of two blood pressure readings was recorded after the subject sat for about 10 min. Fifty age-matched non-diabetic apparently healthy volunteers (30 males and 20 females) living in Calabar municipality were used as controls in this study. They were selected from blood donors, staff of University of Calabar Teaching Hospital and workers of Calabar municipal council. Informed consent was obtained from all the participants.

Seven milliliters (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 revolution per minute 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. The results were expressed as mean ± standard deviation and students' t-test for paired means was used for statistical comparison

RESULT

Table 1 shows the means and standard deviations of the various parameters that were analyzed. The mean fasting blood sugar of diabetic patients 184.14 ± 87.30 mg/100 ml, (normal range 63 - 99 mg/100) was significantly higher than that of the control subjects which was 69.48 ± 6.3 mg/100 ml. The mean relative plasma viscosity of diabetics was 1.65 ± 0.08 (normal range, 1.47 - 1.86) and this showed a significant increase ($p < 0.05$) when compared with the control subjects (1.49 ± 0.06). The mean fibrinogen level in diabetics was 5.22 ± 89 g/l, (normal range, 1.5 - 4.0 g/l) and this was found to be significantly higher ($p < 0.05$) than that of the control subjects (2.5 ± 0.65 g/l). The euglobulin lyses time measured in minutes was 268.4 ± 56.9 (90 - 240 min) for the diabetics and was significantly higher ($p < 0.05$) than 147.6 ± 46.96 obtained for the controls.

Table 2 shows mean values of the patients with type I diabetes in comparison with those who had type II diabetes. The values obtained showed no statistical difference ($P > 0.05$). Figure 1 shows a positive and significant correlation between RPV and duration of diabetes among the diabetic subjects ($r = 0.323$, $p < 0.05$). Figure 2 shows a positive and significant correlation between fasting blood sugar and plasma fibrinogen concentration among the diabetic subjects ($r = 0.635$, $p < 0.05$).

Table 3 shows haemorrheologic and fibrinolytic activities among diabetics with respect to presence of hypertension. The diabetics with hypertension had mean relative plasma viscosity of 1.69 ± 0.08 and this showed no statistical difference when compared with 1.64 ± 0.07

Table 2. Haemorrheologic and fibrinolytic activities in (50) diabetics based on type of diabetes mellitus.

Type of DM	RPV	PFC (g/l)	ELT (min)
Type I (N = 16)	1.635 ± 0.07	4.8± 1.97	265.93 ± 55.65
Type II (N = 34)	1.66 ± 0.08	5.41 ± 1.84	269.56 ± 58.41
P value	> 0.05	>0.05	> 0.05

Table 3. Haemorrheologic and fibrinolytic activities among diabetic patients with respect to presence of hypertension.

Subjects	RPV	PFC (g/l)	ELT (min)
Diabetics with hypertension (n = 11)	1.69 ± 0.08	6.27 ± 1.85	278.64 ± 55.05
Diabetics without hypertension (n = 39)	1.64 ± 0.07	4.92 ± 1.81	263.97 ± 58.39
P value	> 0.05	< 0.05	> 0.05

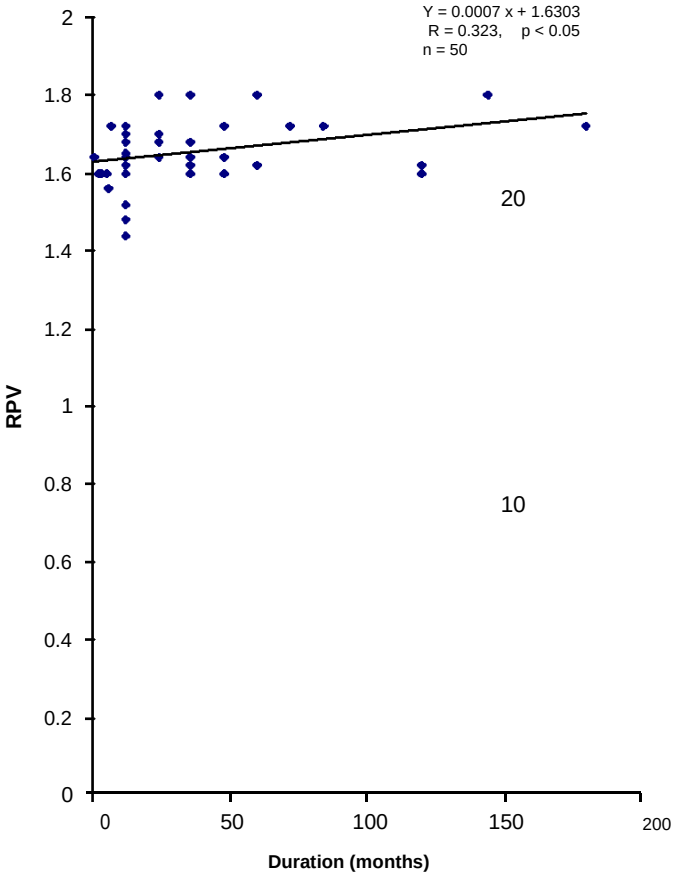

Figure 1. Correlation graph between relative plasma viscosity and duration of diabetes.

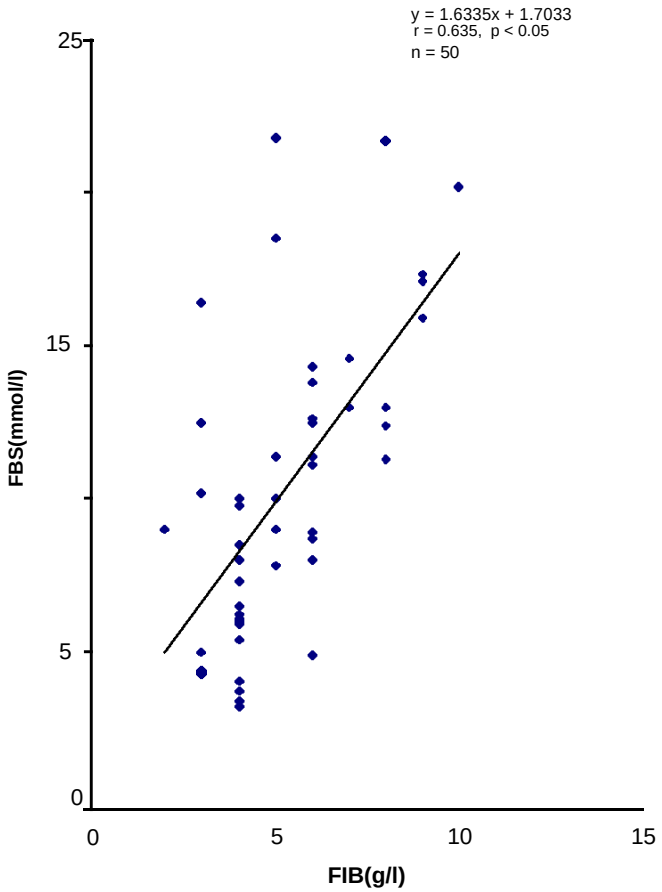

Figure 2. Correlation graph between fasting blood sugar and plasma fibrinogen concentration in diabetic subjects.

obtained for the diabetics without hypertension (p > 0.05). The mean fibrinogen level of diabetics with hypertension was 6.27 ± 1.85 g/l and that of the diabetics without hypertension was 4.92 ± 1.81g/l. There was a significant difference between them (p < 0.05). The mean ELT of diabetics with hypertension was 278.64 ± 55.05 min and this showed no statistical difference (p > 0.05) with 263.97 ± 58.39 min obtained for diabetics without hypertension. Table 4 shows haemorrheologic and fibrinolytic activities among diabetics subjects based on

Table 4. Haemorrheologic and fibrinolytic activities among diabetic patients based on chemotherapy.

Chemotherapy	RPV	PFC (g/l)	ELT (min)
A: Monotherapy (insulin) (n = 3)	1.61± 0.01	4.0± 1.41	253.33 ± 71.12
B: Oral hypoglycaemic agents and insulin (n = 6)	1.63 ± 0.09	5.5± 2.15	271.67 ± 57.07
C: Combination therapy of Oral hypoglycaemic agents (glanil, glucophage) (n = 41)	1.66 ± 0.08	5.39 ± 1.86	272.68 ± 58.16
D: Non diabetics (n = 50)	1.49 ± 0.06	2.50 ± 0.65	147.60 ± 46.96
P value (A vs. B)	> 0.05	>0.05	> 0.05
(B vs. C)	> 0.05	>0.05	> 0.05
(C vs. D)	< 0.05	<0.05	> 0.05
(D vs. A)	< 0.05	<0.05	< 0.05

chemotherapy. The diabetics on insulin injection alone had mean RPV of 1.61 ± 0.01, PFC of 4.0 ± 1.41 g/l, and ELT of 253.33 ± 71.12 min while those on oral hypoglycaemic agents and insulin injection (n = 6) had mean RPV of 1.63 ± 0.09, PFC of 5.5 ± 2.15 g/l, and ELT of 271.67 ± 57. 07 min. Those on oral combination therapy of hypoglycaemic agents alone like glanil and glucophage (n = 41) had mean RPV of 1.66 ± 0.08, PFC of 5.39 ± 1.86 g/l and ELT of 272.68 ± 58.16 min. No significant difference was observed when the parameters were compared in pairs ($p > 0.05$). However when either of the means obtained from the three groups of diabetics were compared with mean RPV (1.49 ± 0.06), PFC (2.50 ± 0.65 g/l) and ELT (147.6 ± 46.96 min) obtained from the non-diabetic subjects, there was significant difference between them ($p < 0.05$).

DISCUSSION

In this study, relative plasma viscosity (RPV), plasma fibrinogen concentration (PFC) and euglobulin lysis times (ELT) were determined in diabetic and control subjects. Significantly increased RPV (1.65 ± 0.08), PFC (5.22 ± 1.89g/l), and prolonged ELT (268.4 ± 56.9 min) were observed 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 implies defective fibrinolysis and hyperviscous plasma states in diabetics. This raised plasma viscosity causes sluggish flow in microcirculation and results in insufficient tissue perfusion, which could predispose diabetics to high risk for peripheral arterial and heart disease (Baker, 1991). The findings in this study also agree with previous work done by Aigbe and Famodu (1999), who observed that increased plasma viscosity may increase the peripheral resistance, thus promoting elevation of blood pressure. This research observed a significant and positive correlation ($r = 0.323$, $p < 0.05$) between RPV and duration of diabetes. The reason for this type of finding may be as a result of the varying plasma protein concentrations at different durations of diabetes. This agrees with the findings of Aigbe and Famodu (1999) who reported that RPV showed inconsistent changes within the first five years but increased there after.

Fibrinogen levels (6.27 ± 1.85 g/l) showed significant increase ($P < 0.05$) in diabetics with hypertension when compared with those who had no hypertension (4.92 ± 1.81 g/l). The hyperfibrinogenaemia and concomitant hyperviscous plasma observed in this study could either play a role in the pathogenesis of the hypertension or be the consequence of the hypertension itself (Reid and Ojogwu, 1992). Infiltration of the vessel wall by fibrinogen due to increased blood viscosity, increased platelet aggregation and thrombus formation and increased fibrin formation are several pathways by which acute or chronic increase in fibrinogen levels can lead to a cardiovascular event (Vinik et al., 2001) however, persistence of fibrin deposited in the vessel wall is believed to play an important role in the development of hypertension. A defective rheology and fibrin clearing mechanisms may contribute to the aetiology of vascular complication in hypertensive patients especially in the long term (Aigbe and Famodu, 1999). Fibrinogen level in this study had a significant positive correlation with fasting blood sugar among the diabetic subjects ($r = 0.635$, $p < 0.05$). Previous studies in the general as well as in smaller populations have also reported positive correlation between plasma fibrinogen and glucose concentrations. It is therefore possible that spontaneous hyperglycaemia contributed to fibrinogen synthesis under basal condition (Festa et al., 2002).

The ELT of diabetics with hypertension was apparently higher (278.64 ± 55.05 min) than that of the subjects with only diabetes (263.97 ± 58.39 min) though no statistical significance was observed. Adediran et al. (2004) had reported prolonged ELT in diabetic population as an additional risk factor for thromboembolic diseases. A defective rheology and fibrin-clearing mechanism may contribute to the aetiology of vascular complications. This study also observed that there was no significant difference in RPV, PFC, and ELT of type I when compared with type II diabetes. The haemorrheologic and fibrinolytic activities in diabetics showed significant difference ($P < 0.05$) when compared with that of control subjects despite chemotherapy. However, when the comparison was made between those on monotherapy (insulin alone) and combination therapy (insulin with oral

hypoglycaemic agents) and those taking combination of oral hypoglycaemic agents only (glanil, glucophage and metformin) no significant difference was observed in all the parameters ($P > 0.05$). The diabetic patients still had increased values in RPV, ELT and PFC when compared with the control subjects despite being on one form of hypoglycaemic agent or the other. This work has given base line values of RPV, PFC and ELT in diabetics and control subjects in this locality. It has also established that there is a significant increase in haemorrheology and reduced fibrinolytic activities in diabetic subjects when compared with the non-diabetic (control) subjects. In conclusion, the study observed higher defective rheology and fibrin clearing in diabetes with hypertension in Calabar. Furthermore mode of chemotherapy plays little or no role on the rheology and fibrin clearing in diabetes. This defective rheology and fibrin clearing seen in diabetes may be contributory factors to the vascular and thrombotic complications usually observed in diabetic subjects.

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