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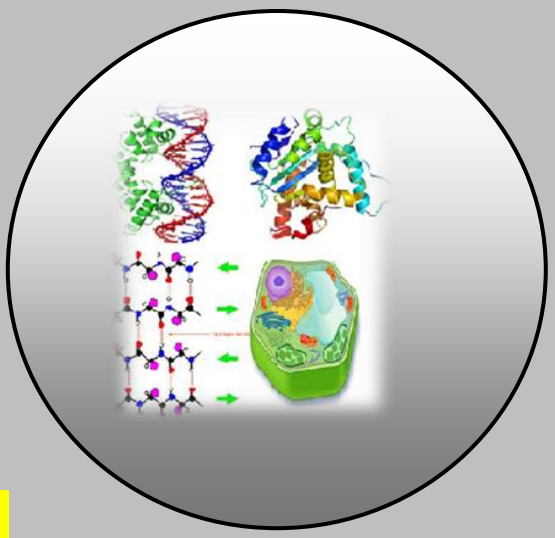

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RESEARCH PAPER

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Correlation of Post-prandial Hyperglycemia with Plasma Fibrinogen and PAI-1 Activity in Diabetics with and without Clinical Evidence of Cardiovascular Disease

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ABSTRACT

In the present study, 60 diabetic patients (type-II) comprising 30 uncomplicated (group-I) and 30 complicated (group-2) i.e. diabetics with cardiovascular disease (CVD), along with 30 healthy age matched controls were investigated for fasting blood sugar (FBS), post-prandial blood sugars (PPBS), lipid profile (serum triglyceride, total cholesterol, HDL-C, LDL-C and VLDL-C), plasma fibrinogen and plasminogen activator inhibitor-1 (PAI-1).

All parameters were significantly elevated in both diabetic groups when compared with controls ($p<0.001$), but on comparing the means value of all parameters of group-1 with group-2 revealed that the values were not statistically significant ($p>0.10$) except the PPBS, plasma fibrinogen and PAI-1 activity were found to be significantly higher in group-2 ($p<0.001$). The correlation coefficient between PPBS and PAI-1 activity was also found significant ($r=0.86$, $p<0.001$). These findings suggest that the post-prandial hyperglycemia could be associated with increased PAI-1 activity which is the major risk factor for macrovascular complications of type-II diabetes.

KEY WORDS – Macrovascular complications, post-prandial, hyperglycemia, plasma fibrinogen and PAI-1.

INTRODUCTION

Diabetes is the most common endocrine disorders characterized by hyperglycemia, glycosuria and a predisposition to chronic complications like retinopathy, nephropathy, and neuropathy

and macrovascular disease. Vascular disease in the Diabetes mellitus is a common problem and mortality due to atherothrombotic disorders is 4-5 times more common in patients with diabetes die a thrombotic death.

One of the major finding in diabetes mellitus is alterations in fibrinolytic system. Euglobin clot lysis time or whole blood clot lysis time which is a global test of fibrinolysis may be normal or prolonged suggesting deficient fibrinolysis at least in a subset of diabetes.

Post-prandial hyperglycemia is well recognized risk factor for the development of both micro and macrovascular complications of diabetes mellitus. The United Kingdom Prospective Diabetes Study (UKPDS) in patients with type-II diabetes have shown that intensive treatment to correct the post-prandial blood sugar that achieves normal blood glucose levels minimized the risk of developing long-term vascular complications of diabetes. Clinical studies have shown an association of elevated plasma PAI-1 activity and increased plasma fibrinogen levels in patients with manifest CVD and with the increased risk of major CVD events in post-prandial state.

The study was aimed to find out the association of post-prandial hyperglycemia with plasma fibrinogen and PAi-1 activity which is the major risk factor for the onset of macrovascular complications in diabetes mellitus.

MATERIAL AND METHODS

The study was conducted between July 2001 to September 2002 in department of Biochemistry, G.R. Medical College and J.A. Group of Hospitals, Gwalior (M.P.). The controls consisted of 30 normal healthy persons of age-group 30-60 years. The diabetic cases were divided into group-1 and group-2 of age-group of 30-60 years. Group-1 comprised of 30 patients of type-II diabetes without and complication and group-2 comprised of 30 patients of type-II diabetes with clinical evidence of cardiovascular disease (macrovascular complication).

All cases were diagnosed by history and clinical evaluation by physician and all the samples were analysed in the post-prandial state (after 2 hours of OGTT). The fasting blood sugar was estimated after a 12 hours overnight fast to confirm diabetes. The body mass index (BMI) was calculated by using the formula, BMI=Weight (kg)/Height $(m)^2$.

The estimation of FBS and PPBS was done by glucose oxidase method. Total cholesterol (TC) and HDL-C were estimated by CHOD-PAP method. Serum triglyceride (TG) was estimated by GPO-PAP method. The values of LDL-C and VLDL-C were calculated using Friedwald's formula: LDL-C=TC- (HDL-C + TG/5), VLDL-C = TG/5. Plasma fibrinogen was estimated by lempert's method and plasma PAi-1 activity was measured by a commercial kit method (Diagnostica Stago, Seine, France). During study all ethical norms are kept in mind. Written consent of the subjects was also taken before starting study.

The data were analysed by using software. Significance of values was calculated by student's "t" test (independent "t" test). The Pearson's correlation coefficient test was performed to determine the correlation among risk factors.

RESULTS

For the study, cases were selected between age group 30-60 years. The BMI was normal in all study groups (Table 1). Average duration of disease in both group-1 and group-2 was 3.93± and 5.50± 4.01 years respectively (table 1).

The biochemical characters of the study groups in post-prandial state are shown in table table 2. All parameters were found significantly higher ($p<0.001$) except HDL-C in both study group of diabetic subjects when compared with controls. Further on comparing the mean values of all parameters of group-1 and group-2, no significance was observed in FBS ($p>0.10$), lipid and lipoproteins ($p>0.10$) but PPBS, PAi-1 activity and plasma fibrinogen were found significantly high ($p>0.001$).

Table 3 showing the Pearson's correlation, coefficient among the PPBS, lipid profile, plasma PAI-1 activity and plasma fibrinogen. A strong correlation between PPBS and PAI-1 activity was noted ($r=0.86$, $p<0.001$) while plasma fibrinogen was not found correlated significantly with PPBS ($r=0.27$, $p>0.10$). A non-significant correlation was also observed between lipid profile and fibrinolytic factors.

DISCUSSION

Type-II diabetic patients with macrovascular disease (CHD) had higher levels of fibrinolytic diabetics. Type-II diabetes is generally considered a hypercoagulable state attributable to enhanced coagulation and impaired fibrinolysis as well as platelet hyperaggregability and endothelial dysfunction.

In people with type-II diabetes, a primary defect is the loss of early insulin secretion, ultimately resulting post-prandial hyperglycemia and mealtime glucose spikes, which have been referred to as the new hidden threat in diabetes. Research has also indicates that in contrast to asymptomatic fasting hyperglycema, asymptomatic glucose spikes are an independent and progressive factor for morbidity and mortality from cardiovascular and cerebrovascular disease. The results of the present study show an association of post-prandial hyperglycema with increased plasma PAI-1 activity. In the post-prandial state, an acute rise in blood sugar favours nonezymatic glycation of plasminogen and makes the molecule less suspectable to activation by tissue plaminogen activator. Under these conditions endothelial cells show an increased secretion of tissue plasminogen activator and a far greater increase in PAI-1, the major inhibitory protein for fibrinolysis leading to a net depression of fibrinolytic activity.

Hyperlipidemia, i.e. elevation of blood lipids is believed to be an important risk factor for coronary heart disease in diabetics. In our study, the lipid profile was found to be elevated significantly in both groups of diabetics in post-prandial state when the results were compared with controls (table 2). A non significant correlation was observed between lipid profile and fibrinolytic factors (table 3). There is evidence of clearance defect contributing to post-prandial hyperlipidia. Defective post-prandial lipoprotein lipase action could account for both fasting and post-prandial hypertriglyceridemia.

Fibrinogen was first reported to be an independent risk factor for myocardial infarction and CAD mortality over a decade ago. Due to strong association of fibrinogen with blood viscosity and thrombus formation, circulating levels of fibrinogen has been known to have a strong and consistent relationship with CHD (both with and without diabetes).

Table 1. Physical characteristics of study groups.

Parameters	Normal healthy	Type-II diabetics	Type-II diabetics
	controls	without CVD (Group-1)	with CVD (Group-2)
	n=30	n=30	n=30
Age (years)	32.53± 7.94	49.59 ± 6.74	53.03 ± 7.20
Duration of diabetes	-	3.93 ± 2.03	5.50 ± 4.01
(years)			
Male: Female ratio	20:10	17:13	18:12
Body mass index	23.7 ± 3.5	25.6 ± 3.5	24.8 ± 5.1

Values are expressed as mean ± SD

Table 2. Biochemical characteristics of study groups in post-prandial state.

Parameters	Normal healthy controls n=30	Type-II diabetics without CVD (Group-1) n=30	Type-II diabetics with CVD (Group-2) n=30
FBS (mmol/l)	4.36 ± 0.33	5.30 ± 0.76***	5.69 ± 1.55***#
PPBS (mmol/l)	6.32 ± 0.55	10.21 ± 1.06***	12.22 ± 3.23***
Serum triglyceride (mmol/l)	1.32 ± 0.21	2.33 ± 0.69***	2.59 ± 0.67***
Total cholesterol (mmol/l)	4.68 ± 0.52	6.17 ± 1.53***	6.54 ± 1.45***
HDL-C (mmol/l)	1.01 ± 0.10	0.77 ± 0.19***	0.74 ± 0.15***
LDL-C (mmol/l)	3.07 ± 0.52	4.34 ± 1.54***	4.63 ± 1.42***
VLDL-C (mmol/l)	0.60 ± 0.09	1.06 ± 0.31***	1.18 ± 0.30***
Plasma fibrinogen (mmol/l)	2.33 ± 0.24	3.10 ± 0.41***	3.98 ± 1.25***#
Plasma PAI-1 activity (IU)	6.57 ± 0.44	10.81 ± 0.85***	12.92 ± 0.58***#

Values are expressed as mean ± SD, *** p<0.001 when compared to controls, # p<0.001 when compared to group-1.

In the present study plasma fibrinogen was also found elevated in both diabetic groups (group-1 and group-2) but no correlation was found between post-prandial hyperglycemia and plasma fibrinogen. This suggests that plasma fibrinogen is an independent risk factor which seems to confer strongest risk for cardiovascular disease followed by PAI-1 activity.

Therefore it is concluded that the post-prandial blood sugar is strongly correlated with PAI-1 activity rather than plasma fibrinogen and hyperlipidemia, which is the major risk factor for the onset of CVD in type-II diabetes.

Table 3. Correlation of PPBS and lipid profile with plasma Fibrinogen and PAI-1 activity in post-prandial state of group-2 diabetic subjects (n=30).

Variables	TG	TC	HDL-C	LDL-C	VLDL-C	Fibrinogen	PAI-1
PPBS	-	-	-	-	-	0.27^{NS}	$0.86^{\#}$
TG	-	-	-	-	-	0.26^{NS}	0.27^{NS}
TC	-	-	-	-	-	0.22^{NS}	0.23^{NS}
HDL-C	-	-	-	-	-	0.27^{NS}	0.28^{NS}
LDL-C	-	-	-	-	-	0.19^{NS}	0.20^{NS}
VLDL-C	-	-	-	-	-	0.21^{NS}	0.22^{NS}
Fibrinogen	-	-	-	-	-	-	0.28^{NS}

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