Original Research Article

Correlation of plasma fibrinogen and lipid profile in normotensive type 2 diabetes and type 2 diabetes with hypertension

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Abstract

Background & Objectives: Diabetes mellitus (DM) is the most common metabolic disorder associated with several abnormalities like hyperglycaemia, high blood pressure, dyslipidaemia, obesity, which often may lead to atherosclerotic cardiovascular disorders. Plasma fibrinogen as an independent cardiovascular risk factor and it is elevated in response to factors like BMI, diabetes, hypertension, serum lipoproteins. The present study has been undertaken to correlate plasma fibrinogen level with cardiovascular risk factors such as BMI, Hypertension, Hyperglycemia and dyslipidaemia, in normotensive as well as hypertensive diabetic patients. **Methods:** A case control study was done with 90 subjects divided into 3 groups (Group 1: healthy controls, Group 2: Normotensive Type 2 Diabetics and Group 3: Hypertensive Type 2 Diabetics) with inclusion and exclusion criteria. Plasma fibrinogen, Fasting and post prandial blood glucose along with fasting lipid profile were estimated. Blood pressure was recorded and BMI was calculated. Multiple comparisons were made using ANOVA test and correlated with Pearson's correlation coefficient 'r'. **Results:** Plasma fibrinogen, BMI were significantly elevated in Group 2 and highest in group 3. Mean ± SD in group 2 and 3 for lipoproteins were respectively, total cholesterol, (156.43± 50.29, 170.70 ± 47.43) HDL, (30.83±7.905, 25.13 ± 5.316) LDL (80.47 ± 22.14, 90.63 ± 31.60), VLDL (35.33 ± 7.336, 37.70 ± 7.484) TAG (136.63 ± 61.90, 146.26 ± 54.71). Plasma fibrinogen is positively correlated to total cholesterol, LDL and triglycerides which is significant in normotensive diabetics and is positively correlated to BMI, SBP, DBP, TC, LDL, VLDL and TAG in hypertensive diabetic subjects which was statistically significant. **Conclusion:** Plasma fibrinogen is correlated significantly with lipoproteins levels and BMI in hypertensive diabetic patients so it can be considered as a risk factor for atherosclerotic events in such patients and it can be a potential marker for screening diabetic patients who are at risk of developing cardiovascular complications.

Keywords: Fibrinogen, Normotensive and Hypertensive Diabetics, Lipoproteins

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. Diabetes mellitus and hypertension are inter-related diseases that strongly predispose an individual to atherosclerotic cardiovascular disease. Mechanisms contributing to systemic vascular disease in diabetes with hypertension are platelet adhesion and aggregation defects, coagulation and lipoprotein abnormalities[1].

Plasma fibrinogen is an important component of coagulation cascade and there are increasing evidences from epidemiological studies suggesting elevated plasma fibrinogen levels are associated with an increased risk of cardiovascular diseases[1,2]. Increased levels of plasma fibrinogen along with hypertriglyceridemia is commonly observed which may be included as a possibility of coronary artery thrombosis[2].

Hypertensive diabetics tend to develop vascular complications earlier than normotensive diabetics[3]. Hypertension is found in approximately 75% of individuals with type 2 diabetes and potentiates the effects of hyperglycaemia and insulin resistance on endothelial dysfunction and atherosclerosis[4].

Another cardiovascular risk factor often seen in diabetics is dyslipidaemia, which includes both increased triglycerides and low-density lipoproteins (LDL) levels and decreased levels of the "protective" lipoprotein, i.e. high-density lipoprotein (HDL). Insulin resistance contributes to "diabetic dyslipidaemia" by favoring the hepatic production of atherogenic lipoproteins and by suppressing the uptake of circulating lipids in peripheral tissues[5].

This study has been undertaken to assess the correlation of plasma fibrinogen and lipoproteins levels in hypertensive type 2 diabetic patients and its significance, which can be used for early detection and prevention of high-risk complications.

Material and Methods

Study design: Case control analytical study.

Ethics approval: The study was approved by the institutional ethics committee and informed consent was taken from the all participants.

Study location: Investigations were performed at the Department of Biochemistry, Osmania Medical College/ Osmania General Hospital, Hyderabad.

Study duration: December 2014 to May 2016.

Sample size: Case control study was done with 90 subjects which divided into 3 groups:

Inclusion criteria:

- Group 1: Healthy controls in the age group 25-75 years (n=30)
- Group 2: Normotensive type 2 diabetic patients (on medication), in age group of 25-75 years (n=30).
- Group 3: Hypertensive type 2 diabetic patients (on medication), in the age group 25-75 years (n=30).

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Exclusion criteria: Patients with abnormal lipid profile secondary to hypothyroidism, alcoholic liver disease, renal failure, nephrotic syndrome and patients on drugs like glucocorticoids, oestrogen and progesterone and patients with history of familial dyslipidaemia, pregnant women and smokers were excluded from the study.

Methodology

Patient details including age, sex, medical history, onset, duration and complications of diabetes were filled in a proforma. Body mass index (BMI) was calculated according to the established World Health Organization (WHO) criteria[6]. Fasting venous blood samples were collected from all groups, 3ml of blood was collected into serum vacutainer (red cap), 2ml into sodium fluoride vacutainer (grey cap) and 1.8 ml in citrate vacutainer (blue cap). Fasting plasma glucose was estimated in plasma daily from the grey vacutainer by GOD-POD method, Total cholesterol was estimated by Cholesterol oxidase method on daily basis. HDL- cholesterol by Phosphotungstic acid method, serum triglycerides by GPO-Trinder Method, serum VLDL-cholesterol was calculated as TRIGLYCERIDES/5 and serum LDL-cholesterol by using Friedwald's equation, Fibrinogen was estimated in plasma from the blue vacutainer by Colorimetric method using biuret reaction on daily basis[7-13].

Statistical analysis

Data analysis was done using GraphPad Prism software version 8.0 Descriptive results are expressed as Mean ± SD of various parameters in different groups, to assess the significance of the differences observed in the mean values of different parameters observed in the groups studied, the data is subjected to ANOVA test. The significance of difference in mean values of different groups and within the groups is represented by p value, <0.05 is considered as significant. Pearson's correlation was done to assess the correlation between parameters within each group.

Results

The Mean ± SD of all the parameters studied in the total cases were significantly different from those of controls (p<0.05).Plasma fibrinogen was significantly higher in normotensive diabetics [455.2 ± 91.01mg/dL], and highest in hypertensive diabetics [517.1 ± 114.72 mg/dL] compared to controls [319.9 ± 43.04 mg/dl], p = < 0.001 [Table 1].

BMI was significantly higher in Normotensive diabetics [28.9± 4.21] and Hypertensive diabetes [28.3± 4.87], compared to controls [24.5± 2.58], P = <0.001, [Table 1].

The systolic and diastolic blood pressures were significantly higher in hypertensive Diabetics compared to controls [P = <0.001, Table 1].

The serum HDL were significantly lower in patients with hypertensive diabetics and normotensive diabetics compared to controls [P = <0.001, Table 2].

Total cholesterol, Triglycerides and VLDL cholesterols were higher in Hypertensive diabetics and normotensive diabetics compared to controls [P = 0.068, P = 0.08, P = 0.1012 respectively Table 2]

VLDL cholesterol was significantly higher in Hypertensive diabetics and normotensive diabetics compared to controls [P = 0.0005, Table 2]

Plasma fibrinogen level was positively correlated to total cholesterol, LDL and VLDL levels which was statistically significant in normotensive diabetics and, it was also positively correlated to triglycerides in hypertensive diabetic patients which was statistically significant.

Plasma fibrinogen concentration was higher in Normotensive diabetics and highest in Hypertensive diabetics when compared to controls [Figure 1].

Plasma fibrinogen was positively correlated to BMI but was not statistically significant among the various groups [Table 4]

The concentration of plasma HDL-cholesterol was lowest in hypertensive diabetics and comparable in normotensive diabetics [Figure 2].

Total cholesterol concentration was higher in hypertensive diabetics compared to normotensive diabetics [Figure 3].

Plasma triglyceride concentration was highest in hypertensive diabetics and normotensive diabetics compared to controls [Figure 4].

Table 1: One-way ANOVA (two tailed) for parameters in all groups

Parameter	Group 1 Healthy Controls	Group 2 Normotensive Diabetics	Group 3 Hypertensive Diabetics	F value	P value
	Mean±S.D	Mean ±S.D	Mean ±S.D		
Fibrinogen (mg/dL)	319.9 ± 43.04	455.2 ± 91.01	517.1 ± 114.72	39.28	<0.0001
F.P.G (md/dl)	82.4 ± 11.01	151.7 ± 77.61	138.1 ± 64.01	11.83	<0.0001
BMI (kg/m²)	24.5± 2.58	28.9± 4.21	28.3± 4.87	10.85	<0.0001
Age (year)	51 ± 11	51.8± 8.14	56 ± 7.86	2.929	0.0587
Systole (mmHg)	123 ± 5.98	121.8 ± 10.65	135.0 ± 10.07	19.24	<0.0001
Diastole (mmHg)	80.80 ± 5.11	81.1 ± 7.49	87.8 ± 6.88	11.03	<0.0001

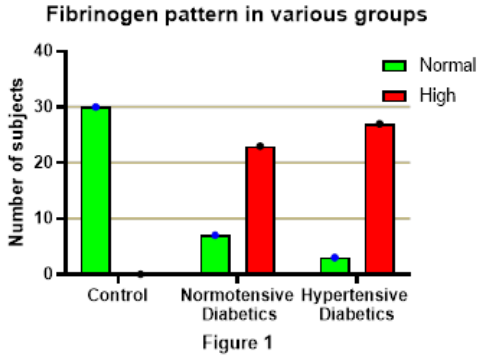

Figure 1

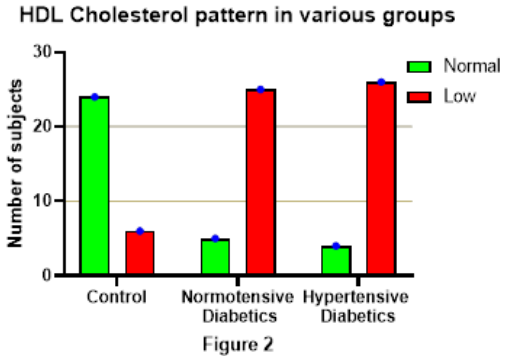

Figure 2

Table 2: One-way ANOVA (two tailed) for lipid profile among various groups

Parameter	Group 1 Controls	Group 2 Normotensive Diabetics	Group 3 Hypertensive Diabetics	F value	P value
	Mean ± S.D	Mean ±S.D	Mean ± S.D		

Total Cholesterol	145.23 ± 23.16	156.43± 50.29	170.70 ± 47.43	2.759	0.0689
Triglycerides	116.87 ± 30.94	136.63 ± 61.90	146.26 ± 54.71	2.598	0.0802
HDL-Cholesterol	41.43 ± 6.89	32.33 ± 7.73	29.53 ± 9.16	57.62	<0.0001
LDL- Cholesterol	80.47 ± 22.14	89.47 ± 37.96	97.53 ± 29.29	2.352	0.1012
VLDL-Cholesterol	23.33 ± 6.21	34.43 ± 18.88	43.20 ± 25.78	8.420	0.0005

Table 3: Pearsons Correlation Coefficient 'r' between Plasma Fibrinogen and lipids

Groups	Lipoprotein	Correlation coefficient 'r'	P value (two tailed)
Controls	Total Cholesterol	-0.03856	0.8397
	Triglycerides	0.1117	0.5568
	HDL-Cholesterol	-0.05721	0.7640
	LDL- Cholesterol	-0.05483	0.7735
	VLDL-Cholesterol	0.1151	0.5446
Normotensive Diabetics	Total Cholesterol	0.5328	0.0024**
	Triglycerides	0.08871	0.6411
	HDL-Cholesterol	0.1894	0.3161
	LDL- Cholesterol	0.4105	0.0243*
	VLDL-Cholesterol	0.4889	0.0061**
Hypertensive Diabetics	Total Cholesterol	0.09755	0.6081
	Triglycerides	0.5025	0.0047**
	HDL-Cholesterol	0.1730	0.3607
	LDL-Cholesterol	-0.1649	0.3837
	VLDL-Cholesterol	0.3203	0.0844

P<0.05, *, ** = Significant

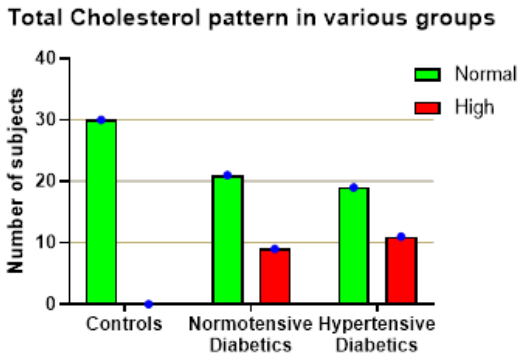

Figure 3

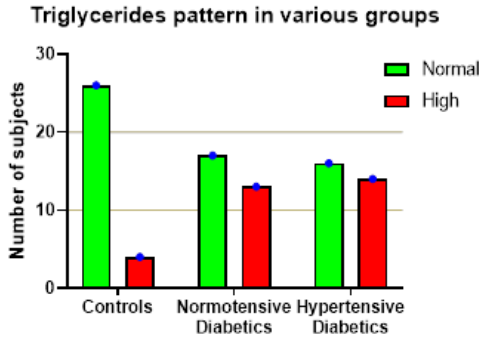

Figure 4

Table 4:Pearsons Correlation 'r' between fibrinogen and BMI

BMI		
Groups	**Correlation coefficient 'r'**	**P value (two tailed)**
Control	0.0009304	0.9961
Normotensive Diabetics	0.03562	0.8518
Hypertensive Diabetics	0.2862	0.1252

P<0.05, *, ** = Significant

Discussion

The rapidly evolving field of medical research for markers of disease severity in chronically ill patients is continuous and necessary. Markers of acute phase reaction, such as C-reactive protein (CRP), Fibrinogen have been reported to be elevated in a number of disease states with inflammatory component. Both in diabetes and hypertensionbackground, inflammation is observed and is linked to underlying number of adverse cardiovascular events associated with these conditions, particularly the development of atherosclerotic plaques[14,15].

In our study, plasma fibrinogen was significantly higher in hypertensive as well as in normotensive diabetics, compared to controls [P = <0.0001, Table 1]. Hypertensive diabetics appeared to represent a subset with more intense inflammatory response; this was evidenced by their higher levels of plasma fibrinogen, compared to controls and normotensive diabetics [Figure 1].

Obesity is an important predisposing factor in the development of insulin resistance and type 2 DM, mainly by increased efflux of free fatty acids from adipose tissues and impaired uptake of free fatty acids by skeletal muscles due to insulin resistance[16]. Obesity is also implicated in the development of hypertension by stimulating renin-angiotensin-aldosterone system[17].In our study, the BMI was significantly higher in hypertensive and normotensive diabetics, compared to controls but there was not much difference between hypertensive diabetics and normotensive diabetics.[P = <0.0001, Table 1].It may so appear from our study that increased BMI contributed more to the development of diabetes than hypertension in our case groups.

Dyslipidaemia is a risk factor to the development of cardiovascular abnormalities in hypertensive diabetics, while HDL-cholesterol is cardioprotective, other non-HDL-cholesterols contribute to vasculopathy, particularly the development of atherosclerosis[18]. In our study serum HDL was significantly lower in normotensive and hypertensive diabetic subjects compared to controls [P= < 0.0001, Table 2]. VLDL cholesterol was found to be significantly elevated in normotensive and hypertensive diabetics when compared to control subjects [P= 0.0005, Table 2]. This implied that hypertensive diabetics had greatest levels of VLDL than normotensive diabetics. An increase in VLDL occurred in diabetes mellitus due to increase availability of glucose for VLDL synthesis and decrease in lipoprotein lipase activity leading to decrease of VLDL from peripheral circulation[19]. There was no significant difference in the means of total Cholesterol, triglycerides, LDL, in both the groups compared to controls.

Our study concluded that type 2 diabetes with concurrent hypertension does not necessarily result in a more severe dyslipidaemia than when either of the two conditions occurring in isolation which could be due to different demographics and study subjects, their lifestyle and geographical and ethnic contrast or use of oral anti hyperlipidaemic drugs.In concordance with our study, Isezue et al. did a cohort study on Nigerian subjects with type 2 diabetes, hypertension, and hypertensive diabetics and reported no significant difference in the means of total cholesterol, LDL-cholesterol, and triglyceride levels among the subject groups[20].

In hypertensive diabetics, plasma fibrinogen had positive correlation only with Triglycerides which was statistically significant, whereas fibrinogen correlated positively with Total cholesterol, LDL & VLDL-cholesterol in normotensive diabetics which was statistically significant.Many factors including reduced blood flow due to elevated viscosity of plasma have been implicated in the pathogenesis of vascular diseases in diabetic patients[3]. The various mechanism by which fibrinogen has been found to promote atherosclerosis and thrombosis are (a) hyperfibrinogenaemia increases plasma viscosity, (b) it induces reversible RBC aggregation, (c) it binds its receptors on platelet membrane and causes platelet aggregation, (d) it forms fibrin and fibrinogen degradation products (FDPs) which in turn bind LDL and sequester more fibrinogen and (e) fibrinogen and FDPs stimulate smooth cell proliferation and migration[21].Taj Muhammad Khan et al, reported that BMI, fibrinogen concentration and plasma viscosity are elevated earlier in hypertensive diabetics than normotensive diabetics, suggesting that onset of the complications may be earlier in hypertensive diabetics and delayed in normotensive diabetics which isin line with our study showing that plasma fibrinogen is elevated significantly in hypertensive diabetics compared to healthy controls and normotensive diabetics.

Conclusion

Plasma fibrinogen correlated well with the BMI, Lipoproteins and Hypertension which are potential markers of cardiovascular risk in those who had diabetes coexisting with hypertension and normotensive diabetics. Thus, it may be used as an additional marker for risk assessment in both normotensive diabetics and diabetic hypertensive patients particularly in those who have dyslipidemia.

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