



A study on role of plasma fibrinogen level as a risk factor for development of various complications in type 2 diabetes patients

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Abstract--- Diabetes mellitus (DM) represents a collection of common metabolic disorders, with main focus being the glycemic control. Increased level of fibrinogen is observed in diabetics and largely reflects elevated hepatic production through the actions of inflammatory cytokines and insulin. In this study, attempt was made to infer the relation of fibrinogen level with various risk factors like glycemic control, smoking, hypertension, obesity, dyslipidemia and different microvascular and macrovascular complications among diabetes mellitus patients. A cross sectional observational study was conducted at medicine department of Dhiraj Hospital, Vadodara. Total of 114 newly diagnosed or known case of the diabetes mellitus patients presenting at outpatient department of the internal medicine department were included during study period i.e. one and half years for the study. The level of fibrinogen as well as presence of various risk factors like smoking, hypertension, obesity, dyslipidemia and different microvascular and macrovascular complications were assessed. Ethical permission taken form the institutional ethical committee. Informed consent was taken from each subject prior to inclusion in the study. The average age of the patients was 55.1 years with male preponderance (62.3%).Smoking, overweight/ obesity, hypertension, uncontrolled diabetes and dyslipidaemia was reported in 54.4%, 30.7%, 41.2%, 28.1% and 60.5% respectively. Microvascular complication like retinopathy, nephropathy and neuropathy was reported in 34.2%, 40.4% and 21.1% patients respectively.Macrovascular complications like coronary artery disease and stroke was reported in 20.2% and 16.7% patients respectively. The mean fibrinogen level was and 441.9±31.1 mg/dl among study participants. Average level of fibrinogen found higher among patients with microvascular as well as macrovascular complication.

Keywords: Aetiology, Fibrinogen, Diabetes Mellitus, Dyslipidemia, glycemic control

Introduction

Diabetes mellitus (DM) represents a collection of common metabolic diseases, with main focus being the glycemic control. DM had a complicated multi-factorial aetiology that includes a complex interaction between genes and environmental factors.^[1] Although the prevalence of both type 1 and type 2 DM is growing fast globally, the prevalence of type 2 DM is greater due to a whopping increase in obesity, decreased physical exercise, ever expanding industrialization and the growing geriatric population^[1]. Chronic hyperglycemia contributes to initiation and occurrence of micro and macro vascular complication in diabetes mellitus.^[2] DM is linked with elevated fibrinogen, increased thromboxane A₂, reduced platelet synthesis of nitric oxide, in addition to increased plasminogen activator inhibitor-1 (PAI-1) release causing inhibition of thrombolysis.^[3] Plasma Fibrinogen is developed in the liver and following activation of the coagulation pathway is transformed to a fibrin monomer (by thrombin) which gradually attaches to neighboring molecules through lateral aggregation, forming the blood clot.^[4] The normal range of fibrinogen in the blood is 200-400 mg/dl. Age, gender, habit of smoking, consuming alcohol, body mass index (BMI), high blood pressure, dyslipidemia and glycemic control are various modifiable and non-modifiable determinants.^[5] The higher level of the plasma fibrinogen is associated with the increased chance of development of the cardiovascular disease which found related to the increasing age, high BMI, reduced physical inactivity, diabetes, and habit of smoking.^[6] Keeping this into the thought and because of scarcity of comparative investigations, this study has been done to know the fibrinogen as determinant in type 2 DM for microvascular and macrovascular complication and its relation with glycemic control.

Materials and Methods

A cross-sectional study of 114 patients was done in the department of general medicine at Dhiraj hospital, Vadodara. All participants included in this study underwent complete history taking including symptoms of present illness, co-morbidities, details of causes, risk factors, past history, personal history, and drug history and were subjected to complete examination. Routine investigations like CBC, RFT, LFT, Fasting blood sugar, Post prandial blood sugar, Serum HBA1C, serum electrolytes, urine routine and microscopy, ECG, chest X-ray, and plasma Fibrinogen levels were done.

Results

In the present study, 114 patients were taken for study. The average age of the patients was 55.1 ± 7.9 years. The majority of the patients (87, 76.3%) had age more than 50 years. Out of all patients, 5 (4.4%) patients had age less than 41 years while 22 (19.3%) patients had age between 41 to 50 years. Out of all patients, 71 (62.3%) patients were male while 43 (37.7%) patients were female. In this present study, patients' age ranged from 33 to 73 years. The average age of the participants in our study was 55.1 years. Maximum numbers of the patients were from the age group of 51 to 60 years (48.2%). The mean age of the study participant in similar type of study conducted by Razak M et al.^[7] found higher to the present study i.e. 59.04 years among diabetic patients. In another study the average age of the study patients was lower than the present study. In present study male preponderance (62.3%) was observed. Contrast to present study, the proportion of male patients (46%) was lower than the female patients (54%) in study conducted by Razak et al. (one study with male preponderance.) The variation in age and sex distribution in different study might be due to variation in local epidemiology of the diabetes irrespective region.

Table 1: Relation between glycaemic control and the s. fibrinogen level

Glycaemic control	Fibrinogen level (mg/dl)
	Mean ±S.D.
Good (HbA1c <7.0%) (N=31)	416.5±30.3
Fair (HbA1c 7.0-7.9%) (N=51)	442.5±24.7
Poor (HbA1c >7.9%) (N=32)	465.4±20.9
P value	<0.0001

The mean fibrinogen level was higher among patients who had poor (465.4±20.9 mg/dl) glycaemic control as compare to patients who have fair (442.5±24.7 mg/dl) or good (416.5±30.3 mg/dl) glycaemic control. The correlation of glycemic control with the level of fibrinogen could be due to differential protein synthesis which include reduced synthesis of albumin (29%) and increased synthesis of fibrinogen (50%). The glycosylated fibrinogen is less prone to plasmin depletion, which may be due to insulin-related deficiency among patients with diabetes mellitus.^[61] The results presented by Ganda OP et. al.^[8] report shown that the level of the fibrinogen often are higher in diabetes, irrespective to the diabetes period but particularly among patients with type II diabetes mellitus and pre- existing microvascular and macrovascular complications. No significant relation was found in their study between fibrinogen and plasma sugar levels or glycosylated hemoglobin levels. These findings are similar to the present study. Fibrin degradation products were found elevated markedly in patients with moderate or poor glycemic control diabetic patients by McMillan et al. Bemde AS et. al.^[8] reported that diabetics patients had a higher HbA1c when compared to normal range (4.2–6.2%) of value. The positive correlation was reported between glycosylated hemoglobin level and serum fibrinogen among the diabetes mellitus patient in their study i.e., poorer the glycemic status, higher the fibrinogen levels, the findings were comparable with the present study.

Table 2: Relation between dyslipidaemia and the s. fibrinogen level in patients.

Dyslipidaemia	Fibrinogen level (mg/dl)	P value
	Mean± S.D.	
Present (N=69)	456.2±22.2	0.0001
Absent (N=45)	419.9±30.2	

The average fibrinogen level was higher among patients with dyslipidaemia (456.2±22.2 mg/dl) as compare to the patients with normal lipid profile (419.9±30.2 mg/dl). This difference was statistically significant. Lawrence A et. al.^[9] found the mean HDL level 41.5 ±17.6. Which was lower than the present study that was 48.4 ±3.6. In present study, average fibrinogen level was found 441.9. While study done by Bemde AS et. al.^[8] found 656 mean fibrinogen level. There could be various way to develop hyperfibrinogenemia in patients with diabetes mellitus. There are increase in a number of coagulation factors including fibrinogen in relationship with macrovascular and microvascular disease and status of the glycemic control.

Alao et al^[67] showed elevated levels of TC, HDL, LDL and triglycerides in diabetics compared to controls (no diabetes); in particular, elevated LDL was a major risk factor for coronary artery thrombosis, which confirmed that patients with diabetes mellitus were predisposed to dyslipidemia, with higher risks for vascular disorders. The hypercoagulable state has also been suggested as a potential risk factor.^[10] In present study higher fibrinogen level was recorded in-patient with dyslipidemia. In addition, this association was found statistically significant. In the study, done by Desai VA et.al^[11] and Wilhelmsen L et.al.^[12] also found the comparable result that cholesterol level, serum triglyceride level and LDL level were found to correlate with mean plasma fibrinogen level. As total cholesterol and serum triglycerides level increases plasma fibrinogen level also raises.

Table3 : Relation between s. fibrinogen level and BMI of the patients.

BMI category	Fibrinogen level (mg/dl)	P value
	Mean ±S.D.	
Underweight (<18.5)	368.9±12.1	<0.0001
Normal (18.6-22.9)	441±24.9	
Overweight/ obese (>22.9)	458.20±22.90	

The mean fibrinogen level was 458.20±22.90 mg/dl among overweight/ obese patients, 441±24.9 mg/dl among patients with the normal BMI and 368.9±12.1 mg/dl among underweight patients. The average level of fibrinogen found increasing with increase in BMI of the patients. The difference in average of fibrinogen among these three groups (underweight, normal and overweight/ obese) found statistically significant. The mean BMI of the study participants was 23.43±3.45 in our study, which was lower than the study done by Lawrence A et. al.^[9] They did the study to find out risk factors associated to elevated fibrinogen level and diabetes. The mean BMI of their study was 28.6 ±6.8.

In present study, significantly higher fibrinogen level was found in overweight and obese individuals (high BMI) than the normal individual. Kamath S et. al.^[13] did the review on related risk factors associated with increase fibrinogen level among diabetic patients. They concluded that obesity was influencing factors in increasing plasma fibrinogen level in their study. Ganda OP et.al.^[14] also reported relation between obesity and fibrinogen level among diabetic patients. This association was found highly significant (p<0.0001) in their study which was similar to the present study. The level of fibrinogen was significantly higher among the obese patients as compared to non-obese patients in study done by Bembde AS et al [15] They found higher mean fibrinogen among obese patients (712 ± 114 mg/dl) as compare to the non-obese patients (593 ± 113 mg/dl).

Table 4:Level of fibrinogen in patients with microvascular and macrovascular complication

Complication	Fibrinogen level (mg/dl)
	Mean± S.D.
Retinopathy (N=62)	439.7±31.3

Nephropathy (N=46)	449.8±25.7
Neuropathy (N=24)	458.0±24.2
Coronary Artery Disease (N=23)	469.6±18.5
Stroke (N=19)	477.9±19.3

Above table shows the summary of the average level of fibrinogen in patients with microvascular and macrovascular complication. The average level of the fibrinogen was 439.7 mg/dl, 449.8 mg/dl and 458.0 mg/dl among patients with retinopathy, nephropathy and neuropathy respectively. The average level of the fibrinogen was

469.6 mg/dl and 477.9 mg/dl among patients with coronary artery disease and stroke respectively. In present study, history of coronary artery disease and stroke was reported in 20% and 16% patients respectively. Plasma fibrinogen is an acute-phase protein. The inflammatory process involved in atherosclerotic vascular disease may be part of the explanation for elevated plasma fibrinogen levels in the patient group in the present study. Several large scale prospective studies had recognized fibrinogen as an independent determinant for CAD. [12] Fibrinogen play a vital role in thrombi formation by involving different mechanisms like platelet aggregation, endothelial cell injury, and plasma viscosity and also its higher level is related to the development of plaques [16], and the recurrent angina. In present study fibrinogen level was found more in patient having CAD compare to who have not CAD. In present study s. fibrinogen level found related to the history of CAD. However, the average level of fibrinogen was found higher among patient with stroke but their association was found statistically not significant. Some studies conducted on patients with diabetes mellitus had shown raising prevalence of cardiovascular diseases or other complications related to the diabetes mellitus among patients with high level of fibrinogen and other inflammatory markers. [17,18] In a study done by Coppola et.al. [74], logistic regression model showed that, among diabetes patients, high level of fibrinogen was associated with coronary artery disease. Wilhelmsen L et.al. [9] had analyzed data on levels of coagulation factors and other risk factors like serum cholesterol, blood pressure and smoking to study the possible risk factors for the cardiovascular disease. The myocardial infarction, stroke and mortality was recorded in 92, 37 and 60 patients during the follow up of 13 years. The found weaker relation of fibrinogen with infarction and stroke, when risk factors like serum cholesterol, blood pressure and smoking are taken into the consideration, but still significant relation with stroke reported. Although causation cannot be proven based on these results, there are chances that the level of fibrinogen had plays a role in the development of macrovascular complications like the stroke and myocardial infarction.

Conclusion

Based on present study findings we can conclude that poor glycaemic control, dyslipidaemia and high BMI is related to the fibrinogen level. Serum fibrinogen level is higher among patients with uncontrolled diabetes, high BMI and high cholesterol. The microvascular complication like nephropathy and macrovascular complication like coronary artery disease is related to the high fibrinogen level among patients of diabetes mellitus. This finding can guide clinician to manage patients of the diabetes mellitus on routine basis. Plasma fibrinogen may be used as a screening test for risk stratification in type II diabetes patients alongside investigation like lipid profile.

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