

Original Article

High Fibrinogen Level in Patients with Type 2 DM and Ischemic Cerebrovascular Accident — An Experience From A Tertiary Care Hospital of Eastern India

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Diabetes Mellitus (DM) is a known predisposing factor for development of cerebrovascular accident. Fibrinogen plays a vital role in inflammation, atherogenesis and thrombogenesis which leads to stroke by promoting platelet adhesion and aggregation. A descriptive observational study was done at Murshidabad Medical College and Hospital, Berhampore, Murshidabad, which included 186 patients in 3 groups ie, DM with CVA-62 patients, CVA without DM-54 patients and DM without CVA- 70 patients. Fibrinogen, FBG (Fasting Blood Glucose) and PPBG (Post Prandial Blood Glucose) were tested. The result shows that the mean Fibrinogen level is high in all the group's but highest in DM with CVA group which was statistically significant. High Fibrinogen level is a good prognostic factor. [J Indian Med Assoc 2020; 118(2): 25-7]

Key words : Fibrinogen, Diabetes mellitus, Cerebrovascular accident.

Fibrinogen is a soluble glycoprotein found in the plasma with a molecular weight of 340 K Dalton. As a clotting factor, fibrinogen is an essential component of the blood coagulation system. However, at the “usual” plasma levels of 1.5 to 4.5 gm/L, its concentration far exceeds the minimum concentration of 0.5 -1 gm/l necessary for homeostasis¹.

Fibrinogen plays a vital role in different pathological processes in the body including inflammation, atherogenesis and thrombogenesis. It increases with age, Body Mass Index, smoking, diabetes and post menopause and is related to fasting serum insulin, low density lipoprotein, cholesterol lipoprotein (a) and leukocyte count. Conversely, it decreases with moderate alcohol intake, physical activity, increased HDL cholesterol and hormone replacement therapy².

India, the diabetes capital of the world, has 41 million diabetic. Every fifth diabetic in the world is an Indian. Type 2 Diabetes Mellitus (DM) is the commonest for constituting 90% of diabetic population in our country³. In around 80-90% of subjects with type 2 DM and in approximately 25% of the general population, insulin resistance is found. Levels of fibrinogen is elevated in insulin resistant subjects, an association that suggests a possible role for acute phase cytokines in the abnormalities of coagulation and endothelial function⁴.

Atherosclerosis is the basic pathogenic process in the development of stroke. By using immunofluorescent

Editor's Comment :

- Plasma Fibrinogen may be considered as an important risk factor for Ischemic. Vascular events specially in young and middle aged person.
- Hence, Fibrinogen Level Should be considered during screening programme of risk factor assesment.

technique one study has shown the deposition of fibrinogen in the intima of cerebral arteries and has indicated its role in atherosclerotic process⁵. So in this background we conducted the present study to measure the fibrinogen level in DM patients with or without stroke, to establish the relationship between the level of fibrinogen and stroke.

MATERIAL AND METHODS

This study was a descriptive observational study conducted at the medical inpatient department, outpatient department of Murshidabad Medical College and Hospital during the period from August 2013 to August 2015. Total 186 cases included in this study, out of which 70 were only Diabetes Mellitus (DM), 62 were DM with cerebrovascular accident (CVA), and 54 were CVA without DM. The patients were selected by purposive sampling technique from inpatient department and outpatient department.

All the cases of CVA are confirmed by obvious clinical signs and Non Contract CT scan. Level of fibrinogen in blood was tested by electrochemical clot detection method from a National Accreditation Board for Testing & Calibration Laboratories (NABL) accredited laboratory in Berhampore. FBG and PPBG were tested from Biochemistry department of Murshidabad Medical College.

Exclusion Criteria :

- (1) All hemorrhagic strokes.
- (2) Liver diseases.
- (3) Renal diseases.
- (4) Coagulopathy and sickle cell diseases, thalassemia,

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polycythemia Vera.

- (5) Systemic malignancy.
- (6) Systemic vasculities.
- (7) History of myocardial infarction or majorsurgery within preceding 3 months.
- (8) Patients taking drugs like Bezafibrate, B-blockers, Pentoxifyline and Ticlopidine.
- (9) DKD (Diabetic Kidney Disease)
- (10) NAFLD in DM
- (11) Ischemic cardiomyopathy in DM

OBSERVATIONS

In the present study, out of total 186 patients, 90 (48.4%) were of age group of 61-70 years, 68(36.6%) were of 71-80 years and 28(15%) patients were in the age group of 51-60 years. None of the patients were included in the age group >80 years and <50 years.

In Table 1, $p > 0.05$; signifying that there are no significance in distribution of male and female among different study groups. However, in each group male are more affected than their female counterparts.

In Table 2 result signifies that there are obvious differences in respect to fasting blood glucose among the different study group as p value < 0.05 .

In diabetes with CVA group, the number of patients with $FBG > 200$ mg% are more than the patients with FBG within 126-200 mg%, and the number of patients whose FBG is within 126-200 mg% are more than the patients with $FBG > 200$ mg% in the DM without CVA. This is seen that the number of patients with $PPBG$ within the range of 200-300mg% are more in each study group but the number of patients with $PPBG > 300$ mg% are more in the diabetes with CVA group than in Diabetes without CVA group. So, there is no statistically significant difference in the distribution of $PPBG$ level in two diabetes groups.

The unpaired t test performed between fibrinogen level in DM with CVA group and that of CVA group without DM. The p value is < 0.0001 . The results of unpaired t test between fibrinogen level DM with CVA group and that of DM without CVA group shows the p value = 0.0001. These signifies that difference in the mean blood fibrinogen level between the groups is statistically significant. But the p value is 0.46 when the 2 groups of CVA without DM and DM without CVA are compared, which signifies that difference in the mean blood fibrinogen level between two groups is statistically not significant (Table 3).

The result of an unpaired t-test shows the p value is 0.91 assuming the null hypothesis, signifying that there is no statistical significant difference in the mean of blood fibrinogen level in the male and the female population, though the mean blood fibrinogen level is slightly higher in the female than their male counterpart (Table 4).

Here Pearson correlation coefficient $r = 0.241$ and p value = 0.01. So the rise of mean fibrinogen level with rise of fasting blood glucose is statistically significant (Table 5).

Pearson correlation coefficient $r = 0.240$ and p value = 0.01.

So the change of mean fibrinogen level with post prandial blood glucose is statistically significant (Table 6).

DISCUSSION

As per objective of this study, the mean fibrinogen level was compared among the entire study group. It is found that the mean fibrinogen level is high in all the groups but highest value is seen in Diabetes with CVA group. Similar results observed in one study group of south Asian patients in 2002 as increased fibrinogen and tissue plasminogen activators level in insulin resistant South Asian patients with ischemic stroke⁶. Insulin resistance was significantly higher in stroke patients. Stroke patients showed elevated level of fibrinogen. Higher levels of fibrinogen, von Willebrand factor and tPA in South Asian stroke patients disappeared after adjustments for features of insulin resistance syndrome but persisted after adjustment for presence of diabetes, confirming that these changes are essentially dependent on features of insulin resistance syndrome. In many studies this has been already published that in both the diabetes and the CVA group the mean fibrinogen level is increased. In one study of the department of Medicine, Seth G S Medical College, Parel, Bombay, Maharashtra it is shown that the plasma fibrinogen level is markedly high in the patients of stroke with DM⁷.

As per sex distribution in this study no statistical significance was observed, though in the table no-1, it is shown that in all 3 groups males are more affected.

Table 1 — Distribution of sex in the study group

Study subjects	Male	Percentage	Female	Percentage	Total
CVA with DM	44	70.97	18	29.03	62
CVA without DM	42	80.65	12	19.35	54
DM without CVA	48	64.52	22	35.48	70

Chi square test was done to find the statistical significance between different groups. $\chi^2 = 2.03$, $df = 2$, $p = 0.363$

Table 2 — Distribution of glycemic status in two diabetes group with respect to fasting blood sugar and post prandial blood sugar

Group	Fasting blood glucose			Postprandial blood glucose		
	126-200 mg%	>200 mg%	Total	200-300 mg%	>300 mg%	Total
DM with CVA	26	36	62	44	18	62
DM without CVA	52	18	70	56	14	70

Table 3 — Distribution of blood fibrinogen level in the different study group

Group (Mg/dl)	Mean fibrinogen level	SD
DM with CVA	651.064	123.908
CVA without DM	499.555	67.335
DM without CVA	484.741	87.275

Table 4 — Distribution of mean fibrinogen level in relation to sex

Sex (n=186)(mg/dl)	Number	Mean fibrinogen level	SD
Male	134	544.30	120.39
Female	52	547.46	125.93

Table 5 — Distribution of mean fibrinogen level with rise of fasting glucose

Fasting glucose (mg%)	No of patients (n=186)	Mean fibrinogen level (mg/dl)	SD
<126	54(29.0%)	499.55	67.33
126-176	74(39.8%)	579.95	132.55
177-227	42(22.6%)	566.85	138.75
>227	16(8.6%)	554.56	145.54

Table 6 — Distribution of mean fibrinogen level with rise of post prandial glucose

PPBG (mg/dl)	No of patients N=186	Mean fibrinogen level (mg/dl)	SD
<200	54(29.0%)	499.55	67.33
200-250	32(17.2%)	551.26	119.60
251-300	66(35.5%)	558.47	143.78
301- 350	28(15.1%)	578.15	141.11
351-400	06(3.2%)	572.00	59.39

In the present study, the mean fibrinogen level was higher in the females. Though most of the similar studies showed higher fibrinogen level in female but few studies also failed to demonstrate a significant gender difference in plasma fibrinogen level. The second WHO monitoring trends and determinants in cardiovascular disease Augsburg (MONICA) study found the crude fibrinogen values to be consistently higher in women than men of all ages.

From Table 2, it is clearly observed that in DM with CVA group the number of patients with fasting blood glucose >200 mg% is more than the number of patients with FBG within 126-200 mg% and the number of patients with FBG within 126-200 mg% is more than FBG >200mg% group in DM with CVA. Though the number of patients with PPBG within 200- 300% is more in each group but PPBG >300mg% is more in number in DM with CVA group than DM without CVA group. Seven years follow up study based on prehensive cohorts of non-diabetic and diabetic subjects from Finland demonstrated that the risk of stroke for Noninsulin Dependent Diabetes Mellitus (NIDDM) women were five times more than non-diabetic women, and two to three times in case of man.

The present study showed that the mean fibrinogen level is high with increasing fasting blood glucose and also postprandial blood glucose (Table 5 & Table 6). To evaluate the determinants of elevated fibrinogen levels and the impact of hyperfibrinogenemia on vascular complications in diabetes one study of Joslin Diabetes center, Boston showed the overall fibrinogen levels in diabetic patients were elevated compared with control subjects⁸.

In another study, it has been showed that patients with type 2 DM were having elevated levels of plasma fibrinogen levels (450mg/dl to 980mg/dl) when compared to the normal values (286±67mg/dl) obtained in controls. Plasma fibrinogen levels were higher in hypertensive (831±107mg/dl, 41 pts.) than in normotensives (599±113 mg/dl, 49 pts.)⁹.

It can be concluded that blood fibrinogen level is higher in patients with CVA and co- existent diabetes. However in

many studies it is proved that elevated fibrinogen predicts future ischemic strokes particularly in men and in the young and middle aged and is associated with advanced atherosclerosis¹⁰. Thus, fibrinogen may contribute to better risk assessment in younger and middle aged men, in contribution with established methods.

Plasma fibrinogen levels could be considered for screening program to identify people at high risk of vascular events and attempts should be made to strengthen the treatment of other risk factor in these patients groups¹¹. Future directions require determination of the “critically elevated” fibrinogen level threshold value, development of drugs that would specifically and safely decrease plasma fibrinogen level and conduction of interventional trials to study the influence of lowering fibrinogen levels on overall cardiovascular risk profile.

LIMITATIONS

Hyperfibrinogenemia leads to atherosclerosis and thrombogenesis resulting in ischemic stroke. But comparison between the other factors of atherosclerosis and thrombogenesis ie, Hypertension, Obesity, Smoking, Cholesterol and Hypercoagulable condition is not done in this study. Beside this there is no determined cut off value of hyperfibrinogenemia, so all the cases of high Fibrinogen is taken in this study.

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