

Plasma Fibrinogen Levels in Acute Stroke in Tertiary Care Hospital, Warangal

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Abstract

Introduction: In urban India, stroke accounts for 1% mortality of all hospital admissions, 4% in all medical cases, and about 20% in all disorders of the central nervous system. Risk factor for stroke includes diabetes, hypertension, smoking, and hyperlipidemia, and these have been linked to abnormalities of hemorheology and coagulation such as increased fibrinogen.

Materials and Methods: Plasma fibrinogen of 50 consecutive patients presenting with acute stroke admitted in Mahatma Gandhi Memorial Hospital, Warangal from 2014 February to 2015 July and compared with 50 controls not suffering from stroke with matched age, sex, and risk factors (controls).

Results: The mean age in the present series was 58.52 years for cases and 58.52 years for controls. The youngest age was 35 years. The oldest age was 85 years. The maximum numbers of patients were in the age group 60-69.

Conclusion: The present study involved 50 patients and 50 controls. The mean fibrinogen level among cases was 602.77 mg% and mean fibrinogen level among controls was 301.3 mg%, which are statistically significant. Mean fibrinogen levels in ischemic stroke were significantly higher than hemorrhagic stroke.

Key words: Cardiovascular diseases, Fibrinogen, Ischemic stroke

INTRODUCTION

In urban India, stroke accounts for 1% mortality of all hospital admissions, 4% in all medical cases, and about 20% in all disorders of the central nervous system.¹

Risk factor for stroke includes diabetes, hypertension, smoking, and hyperlipidemia, and these have been linked to abnormalities of hemorheology and coagulation such as increased fibrinogen.¹

Most cerebrovascular accidents are manifest by the abrupt onset of focal neurologic deficit as if the patient is “struck by the hand of the God.”²

Stroke is defined as an abrupt neurologic deficit that is attributable to focal vascular cause. Risk factors for stroke are hypertension, diabetes, hyperlipidemia, obesity, smoking, atrial fibrillation, carotid stenosis, myocardial infarction, and atrial myxomas.²

Epidemiological observations indicate that high plasma fibrinogen levels strongly correlate with two major thrombotic complications of atherosclerosis, stroke, and myocardial infarction. Thrombosis is increasingly recognized as a central mechanism in stroke as well as in myocardial infarction. Fibrinogen is involved in events thought to play a major role in thrombosis.³

Fibrinogen is a soluble plasma glycoprotein that consists of three non-identical pairs of polypeptide chains ($A\alpha$, $B\beta$, and γ chains).⁴

In the first phase of thrombus formation, soluble fibrinogen is converted into insoluble fibrin by thrombin. Thrombin cleaves $A\alpha$ and $B\beta$ chains thereby releasing fibrinopeptides, and these fibrinopeptides initiate a

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process, in which fibrin monomers begin to gel. These fibrin monomers polymerize to form fibrin polymers. This process continues, and elongation of polymers causes formation of protofibrils. Once a critical mass of long protofibrils is established, and the protofibrils form lateral contacts with other protofibrils thereby forming fibrin clot. Fibrin clot thereby potentiates formation of thrombosis.

Epidemiological observations indicate that high plasma fibrinogen levels strongly correlate with the frequency of two major thrombotic complications of atherosclerosis, stroke as well as myocardial infarction. Thrombosis is increasingly recognized as a central mechanism in stroke and myocardial infarction, and fibrinogen is believed to be involved in events thought to play a major role in thrombosis. Therefore, elucidation of the relationship between fibrinogen and thrombosis may strengthen the predictive value of this protein and suggest new treatment in the management of stroke.³

Hence, this study is designed to investigate the association between plasma fibrinogen levels and acute stroke.

MATERIALS AND METHODS

Source of Data

Plasma fibrinogen of 50 consecutive patients presenting with acute stroke admitted in Mahatma Gandhi Memorial Hospital, Warangal from 2014 February to 2015 July and compared with 50 controls not suffering from stroke with matched age, sex, and risk factors (controls).

The study will be carried out on 50 consecutive patients admitted in Mahatma Gandhi Memorial Hospital, Warangal with acute stroke within 24 h of the onset of symptoms. Detailed history will be taken to find out the risk factors such as hypertension, diabetes, smoking, and alcohol consumption.

Hypertension will be diagnosed by the Joint National Committee VII criteria. Diabetes will be diagnosed by the American Diabetes Association criteria. Smoking will be recorded in terms of number of cigarette pack-years smoked. Thorough general and systemic examination will be carried out.

In addition to routine investigations as per standard protocol in the evaluation of stroke patient, fasting plasma fibrinogen level is estimated and compared to age-, sex-, and risk factors-matched controls. Patients will be followed up till they are discharged from the hospital. Controls will be included who are not suffering from stroke and are age-, sex-, and risk factors-matched.

Inclusion Criteria

Patients presenting with acute stroke within 24 h of the onset of symptoms and patients of acute cerebrovascular accident in whom computed tomography scan shows cerebral infarct or hemorrhage were included in the study.

Exclusion Criteria

Patients with evidence of uremia, infection, active hepatic disease, patients who have suffered from myocardial infarction in the past 3 months, patients who have undergone surgery in the past 3 months, pregnancy, patients with high leukocyte count, patients with peripheral vascular disease, patients with chronic atrial fibrillation, and patients with a history of stroke were excluded from the study.

Detailed history, clinical examination, and relevant laboratory investigations were performed as per pro forma both in cases and controls. Fasting plasma fibrinogen was estimated in patients and age-, sex-, and risk factors-matched controls. The plasma fibrinogen was measured quantitatively by the Clauss method. The name of kit used was Dade's Behring fibrinogen estimation kit

Fibrinogen is a plasma protein, which is converted from a soluble protein to an insoluble polymer by action of thrombin resulting in the formation of fibrin clot.

The thrombin clotting time of dilute plasma is inversely proportional to the fibrinogen concentration of the plasma.

Using this principle, Clauss developed a simple quantitative assay for fibrinogen by measuring the clotting time of dilute plasma when excess thrombin is added. The clotting time obtained is then compared with that of a standardized fibrinogen preparation.

Venous blood is collected in an evacuated siliconized blood collection tube containing 1 volume of 0.11 mol/l of sodium citrate (3.8%) and 9 volumes of whole blood, which is centrifuged for 15 min at relative centrifugal force of 2000 g. The buffer which is provided in the Dade Behring fibrinogen estimation kit is used to prepare 1:10 dilution of patient's plasma sample.

ASSAY: 0.2 ml diluted (50 μ l) citrated plasma sample is incubated for 1 min then 25 μ l of thrombin reagent is added at room temperature, and clotting time is then determined at 37° C centigrade using a coagulation instrument. The fibrinogen concentration is then determined by matching the clotting time from the standard provided and prepared in the Dade Behring fibrinogen estimation kit.

RESULTS

Age Distribution

The mean age in the present series was 58.52 years for cases and 58.52 years for controls. The youngest age was 35 years. The oldest age was 85 years. The maximum numbers of patients were in the age group 60-69 (Table 1).

Sex Distribution

Among 50 patients studied, 62% were male and 38% were female. In this study, male: female ratio is 62:38 (Table 2).

Fibrinogen

In the present study, minimum plasma fibrinogen level among cases was 180 mg/dl and minimum plasma fibrinogen level among controls was 130 mg/dl. In the present study, maximum plasma fibrinogen level among cases was 850 mg/dl and maximum plasma fibrinogen level among controls was 680 mg/dl (Table 3).

In present study among cases, mean fibrinogen levels were higher in ischemic stroke than hemorrhagic stroke, which is statistically significant (Table 4).

DISCUSSION

Fibrinogen

The present study involved 50 patients and 50 controls. The mean fibrinogen level among cases was 602.77 mg% and mean fibrinogen level among controls was 301.3 mg%, which are statistically significant.

Mean fibrinogen levels in ischemic stroke were significantly higher than hemorrhagic stroke.

Mistry *et al.* in their study involving 56 patients admitted in the hospital within 24 h of onset of symptoms. The levels were found to be raised significantly (531.73 ± 74 mg%) compared to those of the age- and sex-matched control group (445.78 ± 92.28 mg%).¹

When the levels of plasma fibrinogen in stroke group with one risk factor were compared to those of individuals with comparable control group with same risk factor, a significant difference was observed in hypertensive, smokers, diabetic, and obese stroke groups.

Hazra *et al.* in their study involving 33 patients with cerebral thrombosis and 30 patients with cerebral hemorrhage admitted within 24 h of onset of stroke concluded that the mean plasma fibrinogen concentration in patients with cerebral thrombosis (378.67 mg/dl) is significantly higher when compared to patients with cerebral hemorrhage (224.4 mg/dl) and in the control group (216.67).⁵

Table 1: Age distribution of cases and controls

Age group years	Frequency cases	Frequency controls
30-39	3	3
40-49	11	11
50-59	11	11
60-69	15	15
70 and >70 above	10	10
Total	50	50

Table 2: Sex distribution of cases and controls

Patients	Cases	Controls
Males	31	31
Females	19	19
Total	50	50

Table 3: Plasma fibrinogen levels in cases and controls

Levels	Plasma fibrinogen levels cases (mg/dl)	Plasma fibrinogen levels in controls (mg/dl)
Minimum	180	130
maximum	850	680

Table 4: Mean fibrinogen among ischemic and hemorrhagic stroke

Parameter	Ischemic stroke	Hemorrhagic stroke
Number of patients	45	5
Mean (cases)	646.22	324.00
P	0.02	

Naryanaswamy, Ravi, and Nagarjun in their study involving 30 patients of ischemic stroke and 20 patients of hemorrhagic stroke within 24 h of onset of stroke concluded that mean fibrinogen levels were significantly raised in cases ($411.50 + 111.56$ mg/dl) compared to controls ($313.76 + 71.24$ mg/dl).⁶

In all the above studies, the level of fibrinogen in cases is increased when compared to controls which are statistically significant. The present study has given similar results as compared with the above-mentioned studies; variation in the level of fibrinogen in the above studies may be due to:

- i. Variation in ethnicity
- ii. The method of fibrinogen assay
- iii. Age group and sex of the patient selected for the study (Table 5).

Age and Fibrinogen

Lee⁷ and Maede⁸ have shown that fibrinogen level increases with age. This study also demonstrates an increasing trend of fibrinogen with age.

Table 5: Plasma fibrinogen level in other studies in comparison to our study

Author/study	Study population	Mean fibrinogen cases (mg%)	Mean fibrinogen controls (mg%)	P
Present study	50 cases and 50 controls	602±197.246	301±141.4538	P=0.0
Hazra <i>et al.</i> ⁵	63 cases and 30 controls	378.67	216.67	<0.01
Mistry <i>et al.</i> ¹	56 cases and 40 controls	531±74	445.78±92.28	<0.01
Narayanaswamy <i>et al.</i>	50 cases and 50 controls	(411.50+111.56 mg/dl)	(313.76+71.24 mg/dl)	<0.05

As age advances, there is change in orientation of gpIIb/IIIa receptor causing decreased fibrinolytic activity which accounts for increased plasma fibrinogen levels as age advances. It is likely that mutation accumulation of plasma fibrinogen plays a significant role in the changes of fibrinogen with age. The increase of variance with age is the product of unrepaired evolutionary damage in different levels of organization, and the mutations causes increased fibrinogen levels as age advances.

Sex and Fibrinogen

Lee⁷ and Maede⁸ have shown males have higher fibrinogen when compared to females. This study has shown that fibrinogen was increased in females than males among cases. In controls, males had higher fibrinogen compared to females, which is statistically significant. Higher fibrinolytic activity in females explained the lower fibrinogen levels in females when compared to males.

Smoking and Fibrinogen

Ernst has demonstrated that smoking is associated with increased plasma fibrinogen levels.

This study has shown that among cases, mean plasma fibrinogen levels were increased in smokers when compared to non-smokers. Among smokers, the mean plasma fibrinogen levels were higher in cases when compared to control group. Plasma fibrinogen levels increase with smoking and contribute to stroke. Hence, it can be used to predict the stroke in smokers.

Other studies have demonstrated that in smokers, the plasma fibrinogen is elevated because smoking activates lung macrophages which release IL- β which increases fibrinogen synthesis.¹⁰

Smoking decreases fibrinolytic activity.¹¹ Smoking causes endothelial damage resulting in activation of coagulation system and releases clotting factors.⁸

Hypertension and Fibrinogen

Jain *et al.*¹¹ have demonstrated fibrinogen levels are higher in hypertensives. Lee⁷ has demonstrated plasma fibrinogen was higher among hypertensives. Mistry *et al.* study, within stroke group, hypertensive patients had higher fibrinogen than normotensive patients.¹

In the present study, within stroke group (cases), mean fibrinogen levels are higher in hypertensives than

normotensive patients. Both studies show similar results suggestive of hypertension which contribute to an increase in plasma fibrinogen levels in stroke. Hence, in hypertensive patients, it can be used for prediction of stroke. Several plausible mechanisms could explain an observed association between elevated fibrinogen levels and hypertension,⁹ which is a relation of fibrinogen to increased viscosity and peripheral vascular resistance. Hyperinsulinemia and insulin resistance are common among hypertensives, and hyperinsulinemia is known to cause decreased fibrinolytic activity, hence increased fibrinogen levels in hypertensives.

Markers of inflammation, such as IL-6 and IL-8, are elevated in hypertension and causes reduced consumption of fibrinogen, thereby contributing to increased plasma fibrinogen in hypertension, increased platelet activation, increased activity of coagulation system, and decreased function of the fibrinolytic system.

Diabetes and Fibrinogen

In this study, diabetics had higher mean fibrinogen levels than non-diabetics in both cases and controls.

In Naryanaswamy, Ravi, Nagarjun study among cases, diabetics had higher fibrinogen levels than in non-diabetics, which was statistically significant.⁶ Both studies show similar results suggestive of diabetes which contribute to an increase in plasma fibrinogen levels in stroke; Hence, it can be used for prediction of stroke in diabetics. The exact mechanism of increased fibrinogen levels in diabetics is unknown. Insulin stimulates cholesterol synthesis in smooth muscle cells and macrophages of the arterial walls stimulates the proliferation and migration of smooth muscle cells, which are the possible mechanisms.¹² It also enhances the formation of fibrinogen. Endothelial dysfunction which is common in diabetics, which causes decreased fibrinolytic activity and hence increased plasma fibrinogen levels.

The plasma glucagon concentration is positively related to the plasma fibrinogen concentration. Thus, fibrinogen production is markedly enhanced in diabetic patients, and this alteration is likely to determine the observed hyperfibrinogenemia in these patients. Hyperglucagonemia may contribute to the increased fibrinogen production.

Thus, insulin concentrations (and probably also glucose profiles) may need to be maintained at the lowest attainable

level in type 2 diabetes to prevent increased fibrinogen synthesis and stroke.

Obesity and Fibrinogen

Meade⁸ and Ernst and Resch¹³ have shown that obese individuals have higher fibrinogen levels.

In this study, in cases, obese individuals had higher mean fibrinogen levels compared to non-obese individuals.

CONCLUSION

The mechanisms underlying increased plasma fibrinogen in patients who are overweight.

There is a positive association between obesity (skinfold thickness), plasma insulin concentration, and hyperinsulinemia, thereby stimulating fibrinogen synthesis.

It is possible that the interaction between obesity and physical inactivity may promote dyslipidemia and increased plasma fibrinogen.

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