Plasma Fibrinogen Levels in Uncontrolled Diabetes Mellitus

Dr. Ashna Purushothaman[1], Dr. Premaletha T K[2]

[1](Senior Resident, Department of Physiology, Govt. Medical College, Thiruvananthapuram)
[2](Associate Professor, Department of Physiology Govt. Medical, College, Thiruvananthapuram)

Abstract :
Background: *The increased morbidity and mortality in diabetes mellitus is due to its propensity to develop micro and macro angiopathy. The presence of high levels of plasma fibrinogen is predictive of vascular complications and cardiovascular death in patients with Diabetes Mellitus(DM). The increased prevalence of Coronary Artery Disease (CAD) in diabetic patients makes it important to evaluate changes in plasma fibrinogen along with other cardiovascular risk factors. Methods: This was a hospital based cross sectional study done on 35 diabetic patients withGlycated Haemoglobin(HbA1C)>7%who attended the diabetic clinic under the Dept. of General Medicine, Govt. Medical College, Thiruvananthapuram and an equal number of age and sex matched controls. Biochemical parameters HbA1C, plasma fibrinogen and Random Blood Sugar (RBS) were estimated.*
Results:*Mean plasma fibrinogen level in diabetic patients was 324±55.7mg/dl whereas that in the control group was 213.8±18.8 mg/dl. It was also found that 40% of the diabetics were having plasma fibrinogen levels above 350mg/dl while none among the control group had such high values.A high degree of positive correlation was obtained between plasma levels of fibrinogen with HbA1C levels and with RBS values*
Conclusion:*The increased risk of type 2 diabetic patients to cardiovascular disease and death cannot be fully explained by the conventional risk factors. Fibrinogen may have a role in this excess risk. Therefore plasma fibrinogen may be considered as a marker for early diagnosis and therapeutic interventions*
Keywords: *HbA1C, Plasma fibrinogen, RBS, Uncontrolled DM*

I. Background

Diabetes Mellitus (DM) represents a range of metabolic disorders characterised by hyperglycemia resulting from insulin deficiency, insulin resistance or both. Type 2 DM represents 85% to 95% of the people with diabetes in developed countries and an even higher percentage in developing countries. With over 20 million diabetic people, India leads the world in the number of individuals with Diabetes Mellitus [1]

This disease increases the morbidity and mortality due to its propensity to develop micro and macro angiopathy.[2] Patients with diabetes are prone to arterial thrombosis due to persistently activated thrombogenic pathways and impaired fibrinolysis. The presence of high levels of plasma fibrinogen is predictive for vascular complications and cardiovascular death in patients withdiabetes.[3] Risks of incidence of Coronary Artery Disease (CAD) and fatal CAD are 2 to 4 fold higher in people with DM than in nondiabetics.[4]

Studies have shown that the most common precipitating factor for acute Myocardial Infarction (MI) is formation of an occlusive thrombus on a damaged atherosclerotic lesion. Evidence also suggests that fibrinogen has a role in both early stages of plaque formation and late complications of cardiovascular disease.[5]The excess cardiovascular morbidity and mortality among diabetics have not been fully explained by major risk factors such as dyslipidemiahypertension, and cigarette smoking. Increased attention is being paid to disordered haemostatic mechanism in the pathogenesis of both large vessel and small vessel disease in diabetes.[6]

Fibrinogen plays a vital role in a number of pathological processes in the body, including inflammation thrombogenesis and atherogenesis. The proposed mechanisms include[7] vessel wall infiltration by fibrinogen, haemorheological effects due to increase in blood viscosity, increased platelet aggregation and thrombus formation, augmentation of platelet degranulation etc.The increased prevalence of CAD in diabetes makes it important to evaluate the change in plasma fibrinogen along with other cardiovascular risk factors like total cholesterol, triglyceride, HDL and LDL.[8] The association of plasma fibrinogen levels with vascular disease has made fibrinogen lowering as a therapeutic option.[9]

Plasma fibrinogen levels can be lowered by reducing cigarette smoking, exercise,[10] and in diabetic patients probably by improved metabolic control.[11]So there is a possibility that measurement of fibrinogen may help in disease prediction or prevention. Therefore studies in cardiovascular risk factors in diabetes mellitus should include fibrinogen also as this provide a basis for prevention. Here an attempt is made to study fibrinogen levels in uncontrolled diabetes.

II. Methods

This was a hospital based cross sectional study done on 35 diabetic patients with Glycated Haemoglobin (HBA1C) levels>7%who attended the diabetic clinic under the department of General Medicine, Govt. Medical College Thiruvananthapuram. An equal number of age and sex matched normal individuals were also included for comparison. Study was done for a period of 1 year.

2.1 Inclusion criteria-

Diabetic subjects of both sexes with HbA1C >7 % which is taken as a marker of uncontrolled Diabetes Mellitus.

2.2 Exclusion criteria-
1. Past history of CAD or stroke.
2. Patients previously diagnosed or treated for other heart disease
3. Chronic infection, malignancy

Study began after getting the clearance from human ethical and review board of theinstitution. A written informed consent was obtained from all persons included in the study. Personal and clinical history of each one was taken and Blood Pressure (BP) checked. These were done by oral questionnaire, clinical examination, perusal of clinical records and discussion with concerned physician. Biochemical parameters HbA1C, RBS and plasma fibrinogen were measured.

Target level of HbA1C recommended by ADA(American Diabetic Association) for diabetics under treatment is<7%[12].In this study patients with HbA1C >7% was taken to have uncontrolled diabetes and the comparison group includednondiabetic individuals. Normal fibrinogen level was taken as 350mg/dl[13]

II. Statistical Analysis

The data were entered into a personal computer using the package Microsoft Excel. For analysis SPSS (Statistical Package for Social Sciences) of Window version 17 was used. Continuous variables were expressed as mean ± standard deviation and qualitative data was expressed as percentage. Independent t test was used for comparing quantitative data between groups. Categorical variables were compared using Chi square test. A 'p' value <0.05 was considered statistically significant. Correlations between variables were doneusingPearson correlation test.

IV.   Results
Mean plasma fibrinogen levels in diabetic patients compared to non diabetic comparison group.

Mean plasma fibrinogen in the diabetic patients was 324.4±55.7 mg/dl and that in non diabetic group was 213.8±18.8 mg/dl. This was statistically significant

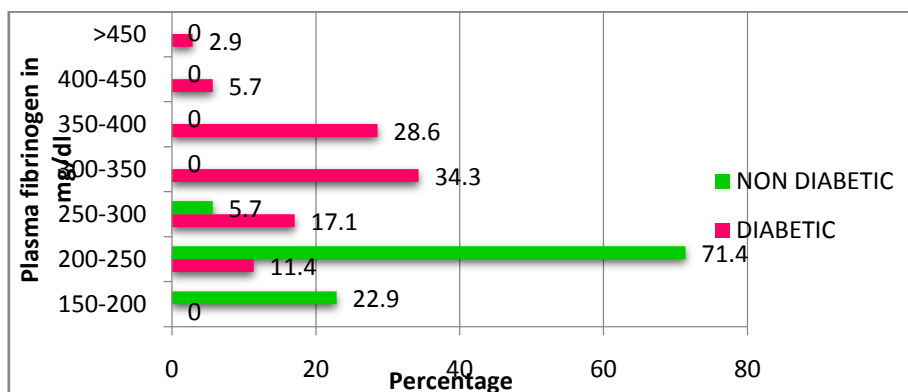**Table 1:** Mean plasma fibrinogen in diabetic patients and non diabetic group

Category	N	Plasma Fibrinogen		t	P
		Mean	SD		
Diabetic	35	324.4	55.7	11.131	<0.001*
Non Diabetic	35	213.8	18.8		
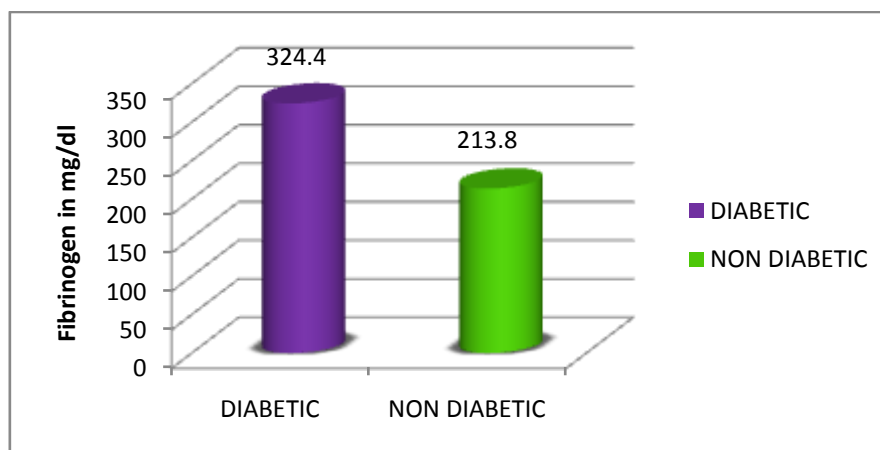
Figure 1: Mean plasma fibrinogen in diabetic patients and non diabetic group

**Table 2:** Distribution of plasma fibrinogen in study population

Plasma .Fibrinogen	Diabetic	Non diabetic	Total
150-200	0 .	8 (22.9%)	8 (11.4%)
200-250	4 (11.4%)	25 (71.4%)	29 (41.4%)
250-300	6 (17.1%)	2 (5.7%)	8 (11.4%)
300-350	12 (34.3%)	0	12 (17.1%)
350-400	10 (28.6%)	0	10 (14.3%)
400-450	2 (5.7%)	0	2 (2.9%)

Figure 2 Distribution of plasma fibrinogen in study population

Table 3: Comparison of diabetic status with plasma fibrinogen

Variable	Category	Diabetics	Non diabetics	P value
Plasma fibrinogen	>350	14 (40%)	0	<0.001*
	≤ 350	21 (60%)	100 (100%)	
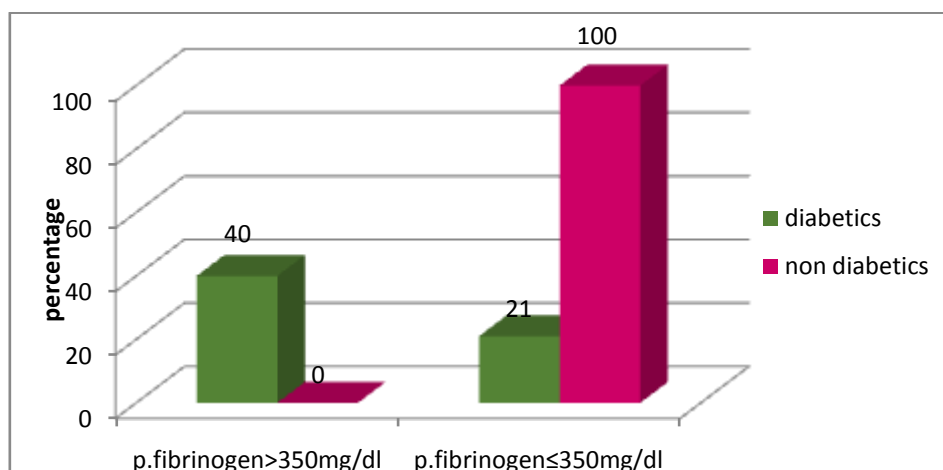
Figure 3: Comparison of diabetic status with plasma fibrinogen

Among diabetics 40% had plasma fibrinogen level above 350 mg% while none in the comparison groupwere having value above 350mg% and the difference in proportion was statisticallysignificant

Correlation of Plasma Fibrinogen with Other Parameters:

Table 4: Correlation of plasma fibrinogen with HbA1C and RBS

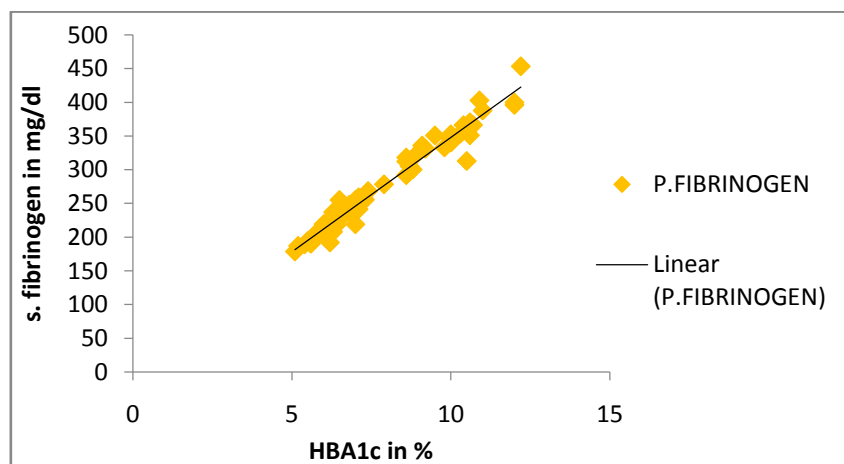| Parameters	Pearson Correlation coefficient (r)	P
Age	0.306	0.010
HbA1C	0.984*	<0.001*
RBS	0.923*	<0.001*

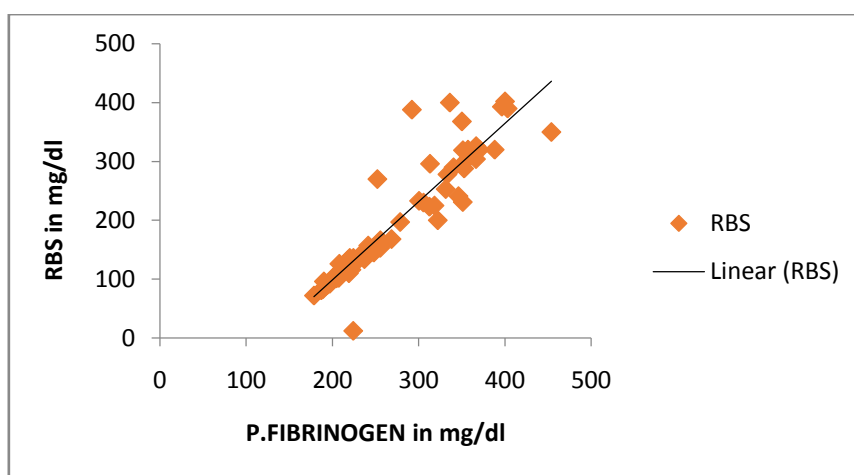**Fig; 4**: Correlation of plasma fibrinogen and HbA1c

Figure 5: Correlation between plasma fibrinogen and RBS

V. Discussion

In the present study it was found that mean fibrinogen level was higher in diabetics and 40% of them had a value above 350 mg% .

There are a number of mechanisms to explain increased fibrinogen levels in DM.

1. Diabetes is associated with low grade inflammation and as a result Interleukin 6 are elevated in these patients. This cytokine stimulates hepatocytes to produce fibrinogen representing an important link between inflammation and hypercoagulation[14]

2. Insulin resistance in type 2 DM is associated with increased hepatic fibrinogen production in response to insulin[14]. Increased fibrinogen synthesis has also been demonstrated postprandially in type 2 DM but not in healthy controls further suggesting hepatic dysregulation of fibrinogen synthesis in this condition[15].

3. In diabetic patients there is increased rate of fibrinogen clearance with shorter fibrinogen circulating half life. This means that the rate of synthesis is even more than that indicated by plasma level.

4. An association between oxidative stress and plasma fibrinogen has been observed in diabetics[16]. Fibrinogen synthesis is regulated by a feedback mechanism by thrombin activation[17] In diabetics thrombin formation is induced by freeradicals [18]. Hyperglycemia and insulin resistance and the consequent oxidative stress may give rise to increased thrombin formation.

Role of plasma fibrinogen in cardiovascular disease risk prediction.

Fibrinogen has been identified as a major independent risk factor for cardiovascular disease. Elevation of fibrinogen may be a pathway by which these risk factors exert their effect. Fibrinogen binds specifically to activated platelets via glycoprotein IIb/IIa contributing to platelet aggregation. Also increased fibrinogen levels promote formation of fibrin. Fibrinogen is a major contributor to plasma viscosity. Finally fibrinogen is an acute phase reactant that is increased in inflammatory states.[19]

Fibrinogen and its metabolites may lead to endothelial dysfunction through various mechanisms.[20] Several atherosclerotic lesions contain large amounts of fibrin. This phenomenon is associated with a decrease

in fibrinolyticactivity and plasminogen concentrations which are observed in CAD.[21] It has been found that fibrin triggers cell proliferation, contributing to cell migration and bonds fibronectin which also triggers cell migration and adhesion.[22] In advanced atherosclerotic plaques, fibrin participates in the cross linkage of LDL and lipid accumulation leading to the creation of the lipid core of atherosclerotic lesions. [21,23] Proinflammatory cytokines such as Interleukin 6 and TNF α are produced from the vasculature, adipose tissue and myocardium; these increase the synthesis of NOand favour leucocyte migration in the sub endothelial space. These also induce liver synthesis of acute phase reactants such as fibrinogen and consequently inflammatory and prothrombotic reactions. Thus fibrinogen participates in the formation of atherosclerotic plaques suggesting that it is a causative factor rather than a result.

The Gothenburg study[24] and Framingham study[25]reported that plasma fibrinogen levels represent an independent risk factor for myocardial infarction and stroke in univariate analysis.

Relation of plasma fibrinogen and glycemic control

In this study there was a high degree of positive correlation between plasma levels of fibrinogen with HbA1C levels and with RBS levels. This shows that as the HbA1C or RBS values increase plasma fibrinogen levels also increases.

Hyperfibrinogenemia in diabetes has been reported to be caused by an increased synthesis of fibrinogen that is not compensated by a proportionate increase in its clearance. This abnormality is associated with insulin deficiency and have been corrected with insulin,[26] suggesting that hyperfibrinogenemia is an expression of poor glycemic control. It has been reported that fibrinopeptide A (apeptide that is released when fibrinogen is transformed into fibrin) is positively related to blood glucose. [27]

Many studies suggested that hyperfibrinogenemia is one way by which hyperglycemia activates coagulation.[28,29] Therefore both epidemiologic and clinical findings support the hypothesis that poor glycemic control may lead to thrombophilia a condition that may be involved in the increased cardiovascular risk in patients with diabetes.

VI. Conclusion

The increased risk ofindividuals with type 2 DM for cardiovascular diseases and deathisnot explained completely by the major conventional risk factors like smoking, hypertension or dyslipedemia. Fibrinogen may have a role in this excess risk. Circulating levels of fibrinogen in diabetes have been known to have astrong and consistent relationship with development of CAD as it reflects increased thrombin formation and therefore a greater probability that a thrombotic event will occur.

In this study a significant increase in plasma fibrinogen levels were found in uncontrolled diabetic patients. This might be one of the risk factors for onset of cardiovascular disease. This also emphasises the importance of assessing this marker for early diagnosis and therapeutic interventions. Lowering fibrinogen could be an important approach to prevention of cardiovascular complications in Diabetics. This may be achieved either by lifestyle modification or by drugs.

Further prospective studies are needed to see whether lowering fibrinogen level per se reduces the occurrence of cardiovascular complications in diabetes mellitus patients. It further needs to be defined their how fibrinogen levels are controlled physiologically and the mechanisms by which therapeutic intervention might decrease it.

Acknowledgement

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