Original Article

Association between Circulating Fibrinogen Level and Severity of Coronary Artery Disease in Type 2 Diabetic Patients with Chronic Stable Angina

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Abstract:

Background: Prevalence of coronary artery disease (CAD) among Bangladeshi population is higher in urban than rural population. Among the conventional risk factors diabetes mellitus is a major concern for Bangladeshi population. Fibrinogen (Fg) in plasma is associated with severity of CAD in some populations with acute coronary syndrome.

Objective: The aim of the study was to find out the correlation between circulating fibrinogen level and severity of coronary artery disease in patients with type 2 diabetes mellitus with chronic stable angina (CSA).

Methods: The study was carried out in the Department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Dhaka from October 2015 to March 2016.Total 132 patients with chronic stable angina (CSA) and type 2 diabetes mellitus who got admitted for coronary angiogram were included in the study and they were divided into 2 groups according to the on admission level of fibrinogen. Coronary angiogram (CAG) was performed in all patients. The severity of the CAD was assessed by angiographic vessel score and Gensini score.

Results: Mean Gensini score was 27.0±22.3 vs 22.2±16.4 and mean vessel score 1.6±0.9 vs 1.2±1.0 in group I and group II respectively (p=0.03 and 0.04, respectively). There was positive correlation between Fg and CAD severity in term of vessel score (r=0.19) and Gensini score (r=0.15). Univariate and multivariate analysis revealed that dyslipidemia, smoking and elevated fibrinogen were the independently significant predictors of severe CAD in type 2 diabetic patients with CSA.

Conclusion: Elevated plasma fibrinogen positively correlates with the severity of CAD in patients with diabetes mellitus having chronic stable angina.

Key Words: *Fibrinogen (Fg), Coronary artery disease (CAD), Vessel score, Gensini score*

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Introduction:

Cardiovascular diseases account for more than 17 million deaths globally each year. It contributes 30% of all deaths. 80% of those occur in low-income and middle-income countries. This figure is expected to grow to 23.6

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million by the year 2030. Coronary artery disease alone caused 7 million deaths worldwide in 2010[1]. Estimates from the Global Burden of Disease Study suggests that by the year 2020 the South Asian part of the world (India, Pakistan, Bangladesh, Nepal) will have more individuals with atherothroembolic cardiovascular disease than any other regions[2].

The exact prevalence of coronary artery disease in Bangladesh is not known. The prevalence of coronary artery disease was first reported in 1976, which was 0.33%. More recent data indicates the coronary artery disease prevalence is 1.85% to 3.4% in rural population and it is 19.6% in an urban population[3]. Three small scale population based studies showed average prevalence of ischemic heart disease (IHD) 6.5 per thousand population of Bangladesh[4]. According to Bangladesh bureau of statistics, 2006 it is the fourth leading cause of death[5].

It is well-recognized that, diabetes mellitus is a powerful independent risk factor for increased cardiovascular mortality associated with coronary artery disease[6,7]. A spectrum of researches attribute coronary atherosclerotic process in a diabetic setting, at least partly due to an imbalance of thrombotic and fibrinolytic system as well as augmented inflammation[8,9].

Fibrinogen (Fg) is a marker of activation of thrombotic system and its plasma level; has been shown to correlate to a certain extent with the development of coronary atherosclerotic lesions, risk of myocardial injury after percutaneous coronary intervention and cardiovascular events in diabetic patients, regardless of platelet aggregation[10,11]. Ridker et al. indicated that elevated serum levels of D-dimer, induced by cleavage of plasmin at the fragment D site of fibrin polymers were related to coronary artery occlusion[12]. Taken together, these observations support a notion that plasma fibrinogen may serve as a mediator linking to thrombotic disease and clinical outcomes.

In a study of Xiong et al. revealed that elevated fibrinogen was independently associated with the presence of significant coronary artery disease[13]. Furthermore, it has been frequently reported that diabetic patients may be clinically asymptomatic even with severe coronary artery disease because of silent myocardial ischemia[14]. The methods for early detection of significant coronary artery disease in diabetic patients have been proven to be elusive, and as a result, prognostic improvement of these patients has not been successfully achieved[15,16]. Therefore, it is necessary to identify early diagnostic biomarkers to improve the clinical outcomes of diabetic patients with coronary artery disease.

There is growing evidence that, elevated plasma fibrinogen is associated with the presence of significant CAD in patients with type 2 diabetes mellitus with chronic stable angina. Plasma fibrinogen as a diagnostic marker of severity of coronary artery disease may have important clinical implications in improving the management strategy and outcome of patients with CSA.

Methods:

This prospective observational study was carried out in the department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Dhaka from October 2015 to March 2016. Total 132 consecutive patients with type 2 diabetes mellitus and chronic stable angina (CSA) full filling the inclusion and exclusion criteria, those admitted for coronary angiogram (CAG) at NICVD were included in the study. Study population was divided into two groups on the basis of serum fibrinogen level, in group I 87 patients with Fg>3.3g/L and in group II 45 patients with Fg<3.3g/L were enlisted.

Patients with Type 1 diabetes, acute coronary syndrome, previous CABG or PCI, chronic heart failure, valvular heart disease, congenital heart disease, hepatic dysfunction, CKD and malignancy were excluded.

Informed written consent was taken from each patient before enrollment. Meticulous history was taken and detailed clinical examination was performed. Risk factors profile including smoking, hypertension, dyslipidaemia and family history of premature coronary artery disease (CAD) were noted. All necessary screening tests for coronary angiogram were done. Resting ECG of all patients was done at a paper speed of 25 mm/s and 10mm standardization at admission using Fukuda ECG machine (Model: FX -2111) Denshi Co Ltd. Japan. Trans-thoracic echocardiography was done by 2D & M-mode and Doppler echocardiography modalities by Accuson X700 ultrasound system, Siemens, Germany. Left ventricular ejection fraction (LVEF) was measured by Tichoitz's method. Blood Sample was taken for fibrinogen before the day of CAG. Fibrinogen measured by automatic system by Stago-Compact Max using STA: Fib-2 reagent using clot based method.

Coronary angiogram was done either by right femoral or right redial route by Trinias C12 unity system, Shimadzu, Japan. All angiography views were evaluated by two experienced cardiologists who were blinded to the study. The severity of the CAD was assessed by Vessel score and Gensini score [17, 18].

From the categorical viewpoint, significant coronary artery disease was defined as > 70% stenosis in any of the three major coronary artery, stenosis <70% in major epicardial coronary arteries were termed non-obstructive CAD. Extent of CAD was defined as insignificant, single, two or three vessel CAD[19]. Score ranges from 0 to 3 were assigned depending on the number of vessels involved. Left main coronary artery was scored as single vessel disease[20].

For severity of CAD the Gensini score system was used. The reduction in the lumen diameter and the roentgen graphic appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion are given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery, X5; the proximal segment of left anterior descending coronary artery (LAD), X2.5; proximal segment of the circumflex artery, X2.5; the mid-segment of the LAD, XI.5; the right coronary artery, the distal segment of the LAD, the posterolateral artery and the obtuse marginal artery X1.0 and others XO.5. This score therefore, places emphasis on the severity of stenosis, while including some of the extent of CAD[21].

Data was analyzed by using SPSS version 21. (Statistical package for social science). Continuous variables were expressed as median or mean ± SD. Categorical variables were expressed as percentage. To test association between Fibrinogen with coronary artery disease severity was done by Pearson's and Spearman's rank order correlation. Univariate and multivariate logistic regression analysis were done to evaluate the independent predictors of severe CAD. The odds ratio (OR) and 95% confidence interval were calculated. Level of significance was p d" 0.05. The study protocol was approved by Bangladesh College of physicians and surgeons. Confidentiality regarding all information's and records was maintained strictly and the patients had the right to withdraw him/her self from the study at any time during the study period.

Results:

The mean age of the study population was 51.9±8.8 years and majority of the study population belonged to 41-50 years age range in both groups (Table I).

Male patients were predominant in both groups. No significance (p=0.22) was found between two groups in terms of sex distribution (Figure 1).

Hypertension, dyslipidaemia and smoking were significant risk factors among the groups, prevalent more in group I patients (Table II).

Table-I

Age distribution of the patient groups

Age Group	Group I (n=87)		Group II (n=45)		Total (N=132)		p value
	Number	%	Number	%	Number	%	
31 – 40	04	4.6	07	15.6	11	8.3	
41 – 50	47	54.0	19	42.2	66	50.0	
51 – 60	22	25.3	13	28.9	35	26.5	
>60	14	16.1	06	13.3	20	15.2	
Mean ± SD	52.7±8.7		50.4±8.7		51.9±8.8		0.14^{NS}

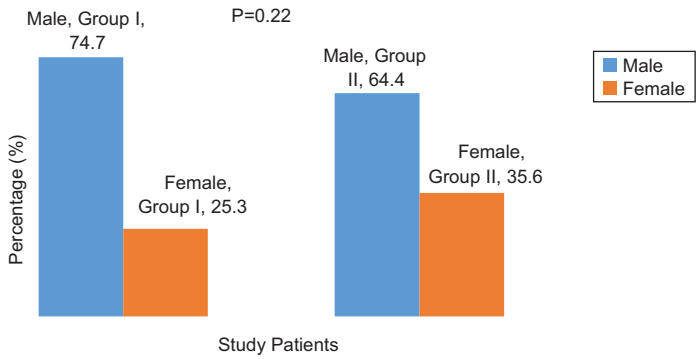

Fig.-1: *Sex distribution among the study groups*

Table-II

Distribution of risk factors in between the study groups

Risk Factors	Group I (n=87)		Group II (n= 45)		p value
	Number	%	Number	%	
Hypertension	58	66.7	21	46.7	0.03^{S}
Dyslipidaemia	42	48.3	11	24.4	0.008^{S}
Smoking	49	56.3	17	37.8	0.04^{S}
Family H/O of CAD	35	40.2	16	35.6	0.60^{NS}

It was found that vessel score 0 was significantly higher in group II than group I (p=0.009). The remaining vessel scores was more in group I than group II (Table III).

Table-III

Distribution of vessel score in between the patient groups.

Vessel Score	Group I (n=87)		Group II (n=45)		p Value
	Number	%	Number	%	
Score - 0	10	11.5	16	35.6	0.009^{S}
Score - 1	34	39.1	11	24.4	0.09^{NS}
Score - 2	29	33.3	12	26.7	0.43^{NS}
Score - 3	14	16.1	06	13.3	0.67^{NS}

There was significant association between Fg (gm/L) and vessel involvement of the study patients (p=0.04). Table IV shows the high sequence of mean Fg (gm/L) of study patients according to the number of vessel involvement.

Table-IV

Association between Fg gm/L and number of vessels involved.

Vessel involvement		Fibrinogen (Fg) gm/L		p value
Type	Number(N=132)	Mean	SD	
No Vessel	26	3.39	0.91	
SVD	45	4.01	0.81	0.04^{S}
DVD	41	4.29	0.65	
TVD	20	4.36	0.82	

Severity of CAD assessed by Gensini score was predominantly higher in group I patients then group II (Table V)..

Table-V

Distribution of Gensini score in between the patient groups.

Gensini Score	Group I (n=87)		Group II (n-45)		p value
	Number	%	Number	%	
Mild (1-10)	16	18.4	05	11.1	0.27^{NS}
Moderate (11-50)	44	50.6	16	35.6	0.03^{S}
Severe (> 50)	17	19.5	08	17.8	0.61^{NS}

The table VI displays the severity of CAD among the study patients. The mean vessel score and Gensini score was statistically significantly higher in group I.

Table-VI

Severity of CAD among the study groups

Severity of CAD	Group I (n=87) Mean ± SD	Group II (n=45) Mean ± SD	p Value
Vessel Score	1.6 ± 0.9	1.2 ± 1.0	0.04[S]
Gensini Score	27.0 ± 22.3	22.2 ±16.4	0.03[S]

There is a positive correlation between Fg and coronary artery disease severity in terms of vessel score (r=0.19). It was observed that the Spearman's correlation statistically significant (p=0.03) by correlation t test (Figure 2).

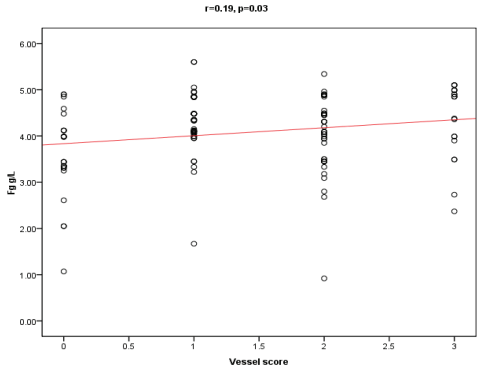

Fig.-2: *Correlation between Fg and vessel score by Spearman's correlation*

There is a positive correlation between Fg and coronary artery disease severity in terms of Gensini score (r=0.15). It was observed that the Pearson's correlation statistically significant (p=0.04) by correlation t test (Figure 3).

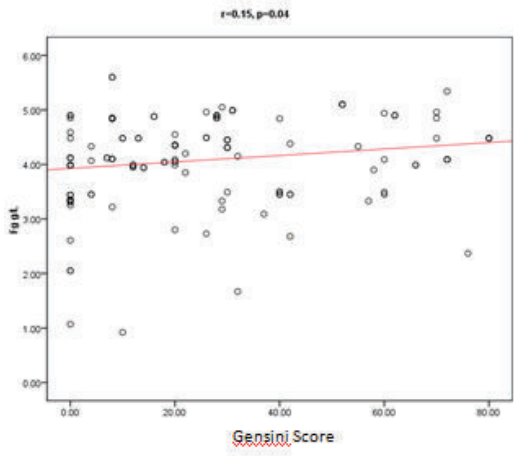

Fig.-3: *Correlation between Fg and Gensini score by Pearson's correlation t-test.*

Univariate and multivariate analysis revealed that out of the 6 variables dyslipidemia, smoking, elevated fibrinogen (Fg) were found to be the independently significant predictors of severe CAD with type 2 diabetic patients (Table VII).

Table-VII

Univariate and multivariate logistic regression analysis of determinants of coronary artery disease.

Variables	Univariate		Multivariate	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age >50	1.89(0.62-4.69)	0.15[NS]	1.37(0.46-3.81)	0.26[NS]
Hypertension	0.81(0.25-2.54)	0.60[NS]	0.70(0.24-2.40)	0.71[NS]
Dyslipidaemia	2.94(1.20-3.79)	0.02[S]	2.54(1.19-3.20)	0.03[S]
Smoking	3.17(1.30-6.15)	0.01[S]	2.70(1.22-5.11)	0.03[S]
Elevated Fibrinogen	1.88(1.30-2.66)	0.001[S]	1.54(1.20-2.46)	0.002[S]

Discussion:

General considerations: This study intended to evaluate fibrinogen (Fg) and its association with severity of coronary artery disease in type 2 diabetes mellitus patients with chronic stable angina. After analyzing the collected clinical and angiographic data and results, it is found that; elevated fibrinogen is associated with presence of significant coronary artery disease.

Coronary artery disease is premature in onset, clinically aggressive and angiographically extensive in South Asians. The underlying etiology and pathophysiology of high prevalence of CAD in Bangladeshis are incompletely understood. Genetic predisposition, high prevalence of central obesity and metabolic syndrome along with conventional risk factors may play important role. Lifestyle related factors, including poor dietary habits, excess saturated and trans-fat, high salt intake and low-level of physical activity may be important as well. Some novel risk factors including hypovitaminosis D, arsenic contamination in water and food-stuff, particulate matter air pollution may also play unique role[3].

Fibrinogen contributes to blood viscosity, platelet aggregation, fibrin formation, and modulates subsequent coagulation activation and fibrinolysis[22,23,24]. Furthermore, fibrinogen participates directly in atherogenesis. Plasma fibrinogen appears to be not only an inflammatory marker linking to thrombotic disease but also a predictor connecting with the cardiovascular events[11].

Thompson et al. found fibrinogen to be a strong predictor of coronary events in patients with angina pectoris[25]. In

those subjects with high total cholesterol, a high fibrinogen level conferred added risk compared with those with low fibrinogen. Patients in the highest fibrinogen quintile had three times the risk of a coronary event than those in the lowest quintile[26].

Subjects with diabetes mellitus have been found to have hyper-reactive platelets. This platelet hyper-reactivity may result in part from increased fibrinogen levels associated with diabetes because fibrinogen acts as a cross bridge between platelets. Poor diabetic control has also been particularly associated with higher levels of fibrinogen and other haemostatic variables[26].

Discussion on the results of the present study:

There was no significant difference of age and sex distribution among the group I and group II. Zaher et al. found the mean age of CAD patients 49.85±9.89 years in Bangladeshi population, which support the finding of the present study[27]. Male patients were predominant in both groups. In a study by Retterstol et al. there was 78.1% male and 21.9% female patients with CAD[28]. Similar result was found by Xiong et al., Hong et al. and Cersit et al. regarding age and gender distribution [28,13,29].

In this study hypertension, dyslipidaemia and smoking had higher statistically significant association in group I patients. Family history of coronary artery disease had similar prevalence in both groups. Previous work in young adults has shown that fibrinogen concentrations are positively associated with BMI, hypertension and cigarette smoking and negatively associated with physical activity and HDL cholesterol[30].

Mean fibrinogen level of study patients according to the number of vessels involvement in none, single, double and triple vessel disease are being 3.39, 4.01, 4.29 and 4.36 respectively. There was significant association between fibrinogen and vessel involvement of the study patients. The no score was significantly higher in group II than group I (p=0.009). The remaining vessel scores were more in group I than group II (p>0.05). So the more vessel involvement was demonstrated in group I than group II and this association was statistically significant (p=0.009). In study by Cersit et al. there was a significant elevation in fibrinogen levels with an increasing number of vessel involvement[29].

According to Gensini scoring system coronary artery disease severity was more in group I than group II. The mean Gensini score was 27.0±22.3 in group I and 22.2±16.4 in group II patients. The difference was statistically significant (p=0.03). The mean vessel score was greater in group I than group II (1.6±0.9 vs. 1.2±1.0) which was statistically significant (p=0.04). In the study by Zhang et al. indicated that patients with high Gensini score had significantly elevated fibrinogen level[32]. Xiong et al. also found that elevated fibrinogen level associated with high Gensini score[13].

In this study there was positive correlation between fibrinogen and coronary artery disease severity in terms of vessel score (r=0.19) and Gensini score (r=0.15) as evidenced by the Spearman's correlation and Pearson's correlation t-test and both are statistically significant. Cersit et al. in their study showed plasma fibrinogen level was significantly higher in patients with stenosis than in patients without stenosis[29]. In the study of Zhang et al. spearman correlation analysis revealed a positive association between fibrinogen level and Gensini score[32]. Xiong et al. also found that elevated fibrinogen level positively associated with higher level of Gensini score[13].

In this study univariate logistic regression analysis of variables likely to cause severe CAD revealed that dyslipidaemia, smoking, elevated fibrinogen were independent predictor of severe coronary artery disease. However, age and hypertension were not independent predictor of severe CAD. In multivariate logistic regression analysis, after adjustment of factors, dyslipidemia, smoking, elevated fibrinogen were found to be the independent predictors of severe CAD. In the study of Zhang et al. multivariate logistic regression analysis demonstrated that plasma fibrinogen level was independently associated with high Gensini score[32]. Hong et al. by multivariate logistic regression analysis found that plasma fibrinogen was an independent predictor of a high Gensini score for diabetic patients[11]. The findings are quite similar and support the results of this study. So, elevated level of plasma fibrinogen is an independent marker of severity of CAD in type II diabetic patients with CSA.

Limitations of the study

This was a single center study that was not representative of the whole country. Measurement of Fg in plasma mainly reflects atherosclerotic process of whole-body vasculature, not specific for coronary arteries. Coronary angiography was evaluated by visual estimation, so there was chance of inter observer and intra observer variation of interpretation of severity of the stenosis.

Conclusion:

The present study demonstrates that elevated plasma fibrinogen is associated with more severe CAD in type 2 diabetes mellitus patients with chronic stable angina.

There is a positive correlation between the plasma levels of fibrinogen and severity of CAD. High fibrinogen level as an early diagnostic marker of coronary artery disease may have important clinical implications in improving the management strategy and outcome of these patients.

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