

Study of fibrinogen in patients with diabetes mellitus

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ABSTRACT

Patients with diabetes mellitus have 2 to 4 times increased risk for cardiovascular disease than non-diabetic patients. However this excess risk is not fully explained by the traditional cardiovascular risk factors (Hypertension, Hypercholesterolaemia, Smoking and Obesity) which are also associated with diabetes. Fibrinogen has been identified as an independent risk factor for cardiovascular disease and it is associated with traditional cardiovascular risk factors. This is a descriptive analytical cross-sectional study carried out in Tribhuvan University Teaching Hospital (TUTH) medical outpatient department and Medical ward from June 2005 to June 2006. A total of 120 consecutive patients were enrolled; 30 patients having Diabetes. Next 30 patients having both diabetes and coronary artery disease. Thirty patients having only coronary artery disease but no diabetes. And 30 patients (control) not having both diabetes and coronary artery disease. Fibrinogen was found to be significantly higher in patients with diabetes than control. Fibrinogen was significantly higher in diabetic patients with coronary artery disease than those patients who had only diabetes or coronary artery disease (p value<0.01).

Keywords: Fibrinogen, diabetes mellitus, cardiovascular disease.

INTRODUCTION

Fibrinogen is the major coagulation protein in blood by mass, the precursor of fibrin and an important determinant of blood viscosity and platelet aggregation. Because fibrinogen level can be reduced considerably by life style interventions that also affect levels of established risk factors (such as regular exercise, smoking cessation, and moderate alcohol consumption) there is possibility that measurement (or modification) of fibrinogen may help in disease prediction or prevention.¹ Studies have shown that formation of an occlusive thrombus on a damaged atherosclerotic lesion is the most common precipitating cause of acute myocardial infarction. Evidence also suggests that, in addition to having a role in the late complications of cardiovascular disease, fibrinogen may be involved in the development of atherosclerotic lesions beginning with the early stages of plaque formation.²

Persons with type 2 diabetes mellitus are at increased risk for cardiovascular-related illness and death, but this excess risk is not completely explained by an increased prevalence of the major conventional cardiovascular risk factors (for example, smoking, hypertension, hypercholesterolemia and obesity). Researchers have suspected that fibrinogen is involved in the excess rate of cardiovascular disease in patients with non-insulin-dependent diabetes mellitus.^{3,4} Clinic-based studies reported that plasma fibrinogen levels were higher in diabetic patients than in controls⁵ and in diabetic patients

with microalbuminuria than in diabetic patients with normoalbuminuria.⁵⁻⁷ Because microalbuminuria has been recognized as a powerful predictor of cardiovascular-related illness and death,⁸ fibrinogen level may be considered a potential additional risk factor in patients with diabetes.

Plasma fibrinogen is influenced by many factors: it increases with age, body mass index, smoking, and diabetes and post menopause and is related to fasting serum insulin, low-density-lipoprotein (LDL) cholesterol lipoprotein (a) and leukocyte count. Conversely, it decreases with moderate alcohol intake, physical activity, increased high-density-lipoprotein (HDL) cholesterol, and with hormone replacement therapy (HRT).⁹⁻¹¹ Fibrinogen plays a vital role in a number of physiopathological processes in the body, including inflammation, atherogenesis and thrombogenesis. Nevertheless, our understanding of the mechanisms leading to the atherothrombotic action of fibrinogen is fragmentary. Proposed mechanisms include the infiltration of the vessel wall by fibrinogen, increase in blood viscosity, increased platelet aggregation and thrombus formation. Furthermore, plasma fibrinogen is also a prominent acute-phase reactant. It augments the degranulation of platelets in response to adenosine diphosphate (ADP), when taken up by the α granules. Thus, elevated concentrations of fibrinogen, perhaps secondary to inflammation or infection (Chlamydia pneumoniae or Helicobacter pylori) implicated in

Table-1: Baseline Characteristics of the Study Population

Characteristics	Patients with DM	Patients with DM+CAD	Patients with only CAD	Control	Total
Number of cases	30	30	30	30	120
Mean age(year)	64.3±11.6	58.1±13.1	61.4±13.7	57.8±11.4	60.5±12.6
Male sex (n)	14	13	14	15	56
Female sex (n)	16	17	16	15	64
Hypertension					
Yes	16	16	13	10	55
No	14	14	17	20	65
Smoke					
Yes	16	19	16	14	65
No	14	11	14	16	55
Alcohol					
Yes	8	7	10	9	34
No	22	23	20	21	86

DM=Patients with Diabetes mellitus, DM+CAD= diabetic patients who also had coronary artery disease, CAD= coronary artery disease, n=number of cases

cardiovascular risk may operate, in part, by increasing the reactivity of platelets.¹²

METHODOLOGY

It was a Descriptive Analytical Cross-sectional study which was conducted in Tribhuvan University Teaching Hospital medical (TUTH) Out Patient Department and Medical Ward from June 2005 to June 2006. First 120 consecutive patients attending TUTH Medical OPD and those who were admitted in Medical Ward were enrolled for the study. 30 cases had only Diabetes. Next 30 patients had both diabetes mellitus and coronary artery disease. Next 30 patients had only coronary artery disease but did not have diabetes. The next 30 patients were apparently healthy looking patients who did not have both diabetes and coronary artery disease (control group). Both fasting and postprandial sugar was measured in diabetes patients. Glycaemic control was assessed by HbA1c in all patients. Serum Fibrinogen was measured by Clauss method.

RESULT

A total of 120 patients were included in the study with 30 patients in each study group as shown in Table-1. The first group included those patients with diabetes mellitus. The second group included those diabetic patients who had coronary artery disease. The third group included those patients who had only coronary artery disease but did not have diabetes. The fourth group included the control patients who did not have both diabetes and coronary artery disease but who attended

the medical OPD or admitted in the medical ward for some other illness. There were 56 male and 64 female patients included in the study. The mean age of study population was 60.5±12.6 years.

Serum fibrinogen was found to be significantly higher in diabetic patients with coronary artery disease than patients with only diabetes or only coronary artery disease. Patients with diabetes or coronary artery disease had significantly higher fibrinogen than the control patients as shown in Table-2.

Serum fibrinogen increases as the glycosylated hemoglobin (HbA1c) increases (P value<0.01). Table-3 shows that the value of fibrinogen is higher in those patients with poorer glycaemic control which is evaluated by HbA1c.

DISCUSSION

The results from our study showed fibrinogen to be significantly higher in diabetic patients who also had coronary artery disease than those who had only coronary artery disease or only diabetes. Our study also showed fibrinogen to be significantly higher in patients with diabetes than the control. James *et al*¹³ found fibrinogen to be higher in diabetic patients than the control. He also showed fibrinogen to be higher in patients with coronary artery disease than without the disease. Our study showed fibrinogen to be significantly associated with the glycosylated hemoglobin (HbA1c). Fibrinogen level increased as the value of HbA1c became higher. We did not find any significant

Table-2: Fibrinogen in the Different Study Groups

Group	Mean fibrinogen (mg/dl)	n
control	216±43	30
DM	341±76	30
DM+CAD	361±68	30
CAD	316±64	30
Total	309±84	120

association between duration of diabetes and fibrinogen level but fibrinogen level was significantly associated with glycaemic control (HbA1c).

Sanchez *et al*¹⁴ conducted a study to assess the prognostic relations between inflammatory markers and mortality in diabetic patients with non ST elevation acute coronary syndrome. They found fibrinogen and WBC count to be higher in diabetic than in non-diabetic patients on admission. Among diabetic patient fibrinogen was higher in those who died during the follow up.

The present study did not find any association between sex and fibrinogen. A study conducted by Jain A *et al* in India also did not show any association between sex and fibrinogen.¹⁵

In the present study Body mass index was found to be significantly associated with fibrinogen. A study by James *et al* also showed fibrinogen to increase with body mass index. Similarly association between body mass index and fibrinogen was shown in study done by Jain A *et al*.

We did not find significant association between waist hip ratio and fibrinogen similar to the study by Richard *et al*.¹⁶ However James J Stec found significant association between waist hip ratio and fibrinogen. We may have got such result as we had taken both the sexes together, but when looked into male and female separately raised fibrinogen was associated with waist hip ratio in male.

Fibrinogen was found to be significantly higher in smokers than non -smokers (p value=0.035). A study conducted by Jing Ma, Charles H *et al* also found fibrinogen to be higher in smokers than non-smokers¹⁷. Similarly James J stec also showed in his study that

fibrinogen was significantly higher in smokers than non smokers.

Our study also showed significant association between history of hypertension and fibrinogen, similar to study by Jing Ma, Charles H *et al* which showed significant association between hypertension and fibrinogen.¹⁷

We found fibrinogen to be lower in those persons who did regular exercise than those who did not (P Value=0.02). In the Caerphilly Prospective Heart Disease Study¹⁸ plasma fibrinogen concentrations were lowered by 0.24 g/l in the third of men who were the most active in leisure activities. Overall, the average decrease achieved by regular endurance exercise over several months was around 0.4 g/l. Men with low level of social activities and activities at home had a higher plasma fibrinogen concentration, when compared to those with high levels of activity.

In the present study fibrinogen was found to be lower in patients who consumed alcohol in moderate amount (P value=0.041) similar to DESIR Study (Data from an Epidemiological Study on the Insulin Resistance syndrome) of 4967 men and women aged 30–64 years, where alcohol consumption was associated with plasma fibrinogen levels, with higher concentrations in those who were non-drinkers or who drank > 60 g of alcohol per day.¹⁹

Our study also showed significant association between total cholesterol and fibrinogen (P value<0.01). A study by Jain A *et al* in India also showed fibrinogen to be associated with total cholesterol. Fibrinogen had inverse association with HDL cholesterol (p value<0.01). A similar association between HDL cholesterol and fibrinogen was shown by James J Stec in his study. We did not find any significant association between LDL cholesterol, triglyceride level and fibrinogen.

Patients with diabetes have increased risk for the development of coronary artery disease. Fibrinogen is found in higher level in patients with diabetes than those patients without diabetes. Fibrinogen is found in higher level in diabetic patients with coronary artery disease than those patients who have only diabetes or only coronary artery disease. Fibrinogen is significantly associated with HbA1C in these patients.

Table-3: Relation between glycosylated hemoglobin A1C (HbA1C) and fibrinogen

HbA1C (%)	Plasma Fibrinogen(mg/dl)	n
4-6.9	276.9±78	80
7-9.9	352.8±55	29
10-13	425.5±20	11

REFERENCES

1. Danish J, Simon G, Thompson D *et al* (Fibrinogen Studies Collaboration). Plasma fibrinogen level and the risk of major cardiovascular diseases and Nonvascular Mortality. *J Amer Med Assoc* 2005; 294:1799-1809.
2. Schwartz CJ, Valente AJ, Kelley JL, Sprague EA, Edwards EH. Thrombosis and the development of atherosclerosis: Rokitansky revisited. *Semin Thromb Hemost* 1988; 14: 189-95.

3. Kannel WB, D'Agostino RB, Wilson P W, Belanger A J, Gagnon D R. Diabetes, fibrinogen and risk of cardiovascular disease: the Framingham experience. *Amer Heart J* 1990; 120: 6726.
4. Lee AJ, Lowe GD, Woodward M, Tunstall-Pedoe H. Fibrinogen in relation to personal history of prevalent hypertension, diabetes, stroke, intermittent claudication, coronary heart disease, and family history: the Scottish Heart Health Study. *Brit Heart J* 1993; 69: 338-42.
5. Ganda OP, Arkin CF. Hyperfibrinogenemia, an important risk factor for vascular complications in diabetes. *Diabetes Care* 1992; 15: 1245-50.
6. Collier A, Rumley A, Rumley AG *et al*. Free radical activity and hemostatic factors in NIDDM patients with and without microalbuminuria. *Diabetes* 1992; 41: 909-13.
7. Schmitz A, Ingerslev J. Haemostatic measures in type 2 diabetic patients with microalbuminuria. *Diabet Med* 1990; 7: 521-5.
8. Knobl P, Schernthaner G, Schnack C *et al*. Thrombogenic factors are related to urinary albumin excretion rate in type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 1993; 36: 1045-50.
9. Neil A, Hawkins M, Potok M, Thorogood M, Cohen D and Mann J. A prospective population-based study of microalbuminuria as a predictor of mortality in NIDDM. *Diabetes Care* 1993; 16: 996-1003.
10. Folsom AR, Wu KK, Davis CE, Conlan M G, Sorlie P D, Szklo M. Population correlates of plasma fibrinogen and factor VII, putative cardiovascular risk factors. *Atherosclerosis* 1991; 91: 191-205.
11. Dotevall A, Johansson S, Wilhelmsen L. Association between fibrinogen and other risk factors for cardiovascular disease in men and women. Results from the Goteborg MONICA survey 1985. *Ann Epidemiol* 1994; 4: 369-74.
12. Schneider DJ, Taatjes DJ, Howard DB, Sobel B E. Increased reactivity of platelets induced by fibrinogen independent of its binding to the IIb-IIIa surface glycoprotein: a potential contributor to cardiovascular risk. *J Amer Coll Cardiol* 1999; 33: 261-6.
13. James JS, Silbershatz H, Geoffrey H *et al*. Association of Fibrinogen with Cardiovascular Risk Factors and Cardiovascular Disease in the Framingham Offspring Population. *Circulation* 2000; 102:1634-8.
14. Sanchez P L, Morinigo J L, Pabon P *et al*. Prognostic relations between inflammatory markers and mortality in diabetic patients with Non-ST elevation acute coronary syndrome. *Heart* 2004; 90: 264-9.
15. Jain A, Gupta HL, Narayan S: Hyperfibrinogenemia in patients of diabetes mellitus in relation to glycemic control and urinary albumin excretion rate. *J Assoc Physicians India* 2001; 49: 227-30.
16. Richard LK, Hunter SJ, Jenkins AJ *et al*. Fibrinogen is a marker for nephropathy and peripheral vascular disease in diabetes. *Diabetes Care* 2003; 26:1439-48.
17. Jing M, Charles H, Hennekens PM, Stampfer MJ. A prospective study of fibrinogen and risk of myocardial infarction in the physician Health Study. *J Amer Coll Cardiol* 1999; 33: 1347-52.
18. Elwood PC, Yarnell JW, Pickering J, Fehily AM, O'Brien JR. Exercise, fibrinogen, and other risk factors for ischaemic heart disease. Caerphilly Prospective Heart Disease Study. *Brit Heart J* 1993; 69:183-7.
19. Mennen LI, Balkau B, Vol S, Cacès E, Eschwège E. Fibrinogen: a possible link between alcohol consumption and cardiovascular disease? DESIR Study Group. *Arterioscler Thromb Vasc Biol* 1999; 19: 887-92.