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Original article

# Study of plasma fibrinogen level in type 2 diabetes mellitus and its association with microalbuminuria and glycemic control

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ABSTRACT

*Objectives:* This study was undertaken to estimate plasma fibrinogen level and its association with microalbuminuria and glycemic control in patients with type 2 diabetes mellitus in addition to assessment of risk factors, such as obesity, hypertension, smoking, and dyslipidemia.
*Methods:* Plasma fibrinogen level (Clauss method) was estimated in 60 type 2 diabetic patients and 30 age, sex, and body mass index matched controls. Plasma fibrinogen level was correlated with various parameters like microalbuminuria (urine albumin to creatinine ratio), glycosylated hemoglobin (ion exchange high performance liquid chromatography), age, sex, body mass index ($kg/m^2$), hypertension, smoking, and dyslipidemia.
*Results:* Mean plasma fibrinogen level in cases was high ($380.03 \pm 101.07$ mg/dl) as compared to controls ($244.43 \pm 61.27$ mg/dl), which was found to be statistically highly significant ($p < 0.0001$). Fibrinogen level was associated with age ($p = 0.003$), body mass index ($p = 0.016$), total cholesterol ($p = 0.003$), LDL ($p = 0.012$), triglycerides ($p = 0.015$), HDL ($p = 0.013$), microalbuminuria ($p < 0.0001$), and glycemic control ($p < 0.0001$) in diabetics. But, no correlation was found with sex ($p = 0.154$), hypertension ($p = 0.167$), duration of diabetes ($p = 0.06$), and smoking ($p = 0.283$) in cases. In controls, plasma fibrinogen level was associated with age ($p = 0.004$) and body mass index ($p = 0.0008$). On multiple linear regression analysis, age ($p = 0.04$), body mass index ($p = 0.038$) and microalbuminuria ($p = 0.008$), were found to be independent variables for hyperfibrinogenemia.
*Conclusion:* Patients with type 2 diabetes mellitus had a higher plasma fibrinogen level. Fibrinogen level was significantly associated with microalbuminuria and glycemic control.


## 1. Introduction

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Patients with type 2 diabetes mellitus have been reported to be at increased risk of developing cardiovascular-related diseases. The increase in cardiovascular morbidity and mortality rates appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors. Individuals with insulin resistance and type 2 diabetes mellitus have elevated levels of plasminogen activator inhibitors (especially PAI-1) and fibrinogen, which enhances the coagulation process and impairs fibrinolysis, thus favoring the development of thrombosis.[1]

Patients with diabetes are prone to arterial thrombosis due to persistently activated thrombogenic pathways and impaired fibrinolysis. The presence of high plasma levels of CRP and fibrinogen are predictive for vascular complications and cardiovascular death in patients with diabetes.[2]

Fibrinogen is a strong and independent cardiovascular risk factor. Its plasma concentration predicts cardiovascular events in both the general population and nondiabetic patients with clinical vascular disease. Plasma fibrinogen may also be increased in type 2 diabetes, thus suggesting that hyperfibrinogenemia could contribute to the excess cardiovascular morbidity and mortality in this disease.[3]

Fibrinogen strongly affects hemostasis, blood rheology, platelet aggregation, and endothelial function. The hemorheological consequences of hyperfibrinogenemia might act at various levels; as follows: by reducing blood flow, by predisposing to thrombosis, and by enhancing atherogenesis.[4]

Microalbuminuria has been recognized as an important biomarker to predict micro- and macrovascular diabetic complications.[5] Poor glycemic control has been reported to be associated with increased vascular complications in diabetics.[6]

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In view of the above concepts and due to paucity of similar studies, this study has been undertaken to study plasma fibrinogen level in patients with type 2 diabetes mellitus and its association with microalbuminuria and glycemic control in addition to assessment of various risk factors, such as age, obesity, hypertension, smoking, and dyslipidemia.

## 2. Methods

The source of data were patients who were known case of type 2 diabetes mellitus attending outdoor or admitted at Govt. medical college and M.B.S. hospital, Kota during the study period from January 2014 to February 2015. Patients of type 1 diabetes mellitus; patients with acute and chronic infections, renal disease, endocrine disease, and malignancy; and patients on warfarin, steroids, and hormone replacement therapy were excluded from the study. Patients with previous history of angina, myocardial infarction or TIA were not included in this study. The method of collection of data was purposive sampling technique and it was a case–control study. Sample size of the cases was sixty patients attending outdoor or admitted at Govt. medical college and M.B.S. hospital, Kota who were diagnosed as type 2 diabetes mellitus, newly detected or already on treatment. Thirty controls were selected from nondiabetic, healthy attendants accompanying the patients at M.B.S. hospital, Kota with no history of diabetes mellitus or hypertension or ischemic heart disease who were age, sex, and body mass index matched to the cases. A detailed history and clinical examination was done pertaining to various risk factors, and relevant laboratory investigations were done in both diabetic patients and in controls. The various parameters that were studied included age of the patient (years), sex, body mass index (kg/m$^2$), smoking, blood pressure (mm Hg), plasma fibrinogen level (mg/dl), glycosylated hemoglobin (%), microalbuminuria, total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride level. Plasma fibrinogen was estimated by clot-based assay, Clauss method.[7] Microalbuminuria was measured by urine albumin to creatinine ratio. Spot urine microalbumin was measured by immunoturbidimetric analysis.[8] Urine creatinine was measured by spectrophotometry. Glycosylated hemoglobin was measured by ion exchange high performance liquid chromatography method.[9] Fasting blood sample was collected for lipid profile. Total cholesterol, LDL, HDL, triglycerides, and plasma glucose were directly assessed by standard enzymatic methods.[10] Blood sugar level, plasma fibrinogen level, microalbuminuria, glycosylated hemoglobin, complete blood count, ESR, C-reactive protein,[11] serum creatinine,[12] and serum lipid profile were measured in cases and controls.

## 3. Results

Fibrinogen levels were correlated with age, sex, body mass index, microalbuminuria, glycemic control, hypertension, smoking, and lipid profile. The patients were divided into four age groups, viz. 41–50 years, 51–60 years, 61–70 years, and 71–80 years, for analytical purpose. According to body mass index, patients were divided in three groups, i.e. 18–25, 26–30, and >30. Mean age of cases was 56.5 years and mean age of controls was 56.2 years. Men and women were equal in number in cases and controls (M:F = 1:1). Mean body mass index was 27.46 in cases and 27.2 in controls. Maximum patients (30) had duration of diabetes more than 5 years with mean duration of 7.5 years. Mean plasma fibrinogen level in cases was high (380.03 ± 101.07 mg/dl) when compared to controls (244.43 ± 61.27 mg/dl) and it was found to be statistically highly significant ($p < 0.0001$) [Table 1].

It was found in cases that as age advances fibrinogen also increases and it was statistically significant ($p = 0.003$). In controls also, fibrinogen showed positive correlation with age ($p = 0.004$). In cases, males had higher mean fibrinogen level than females but it was not statistically significant ($p = 0.154$). In controls also, fibrinogen level did not show significant association with sex ($p = 0.082$). Fibrinogen level showed positive correlation with body mass index in cases ($p = 0.016$) and controls ($p < 0.0001$). Fibrinogen level did not show significant correlation with duration of diabetes ($p = 0.06$) [Tables 2 and 3].

Fibrinogen level was high in patients with microalbuminuria (429.2 ± 93.59 mg/dl) when compared to patients without microalbuminuria (323.8 ± 78.24 mg/dl) and it was found to be statistically significant ($p < 0.0001$). Patients with poor glycemic control had higher fibrinogen level (429.1 ± 94.87 mg/dl) when compared to patients with adequate glycemic control (301.1 ± 45.84 mg/dl) and it was statistically significant ($p < 0.0001$) [Table 2].

In diabetic hypertensive patients, mean fibrinogen level was high when compared to diabetic normotensive patients but it was statistically not significant (395.3 ± 98.37 vs. 358.7 ± 102.92, $p = 0.169$). In smokers, mean fibrinogen level was high when compared to nonsmokers but it was statistically not significant (419.8 ± 126.7 vs. 372.1 ± 94.67, $p = 0.283$) [Table 2].

Plasma fibrinogen levels significantly correlated with total cholesterol ($p = 0.003$), HDL cholesterol ($p = 0.013$), LDL cholesterol ($p = 0.012$), and triglyceride level ($p = 0.015$) [Table 2].

Multiple linear regression analysis was done using Microsoft Excel. On multiple linear regression analysis, age ($p = 0.04$), body mass index ($p = 0.038$), and microalbuminuria ($p = 0.008$) were found to be independent variables for hyperfibrinogenemia [Table 4].

## 4. Discussion

The results from our study showed plasma fibrinogen levels to be significantly high in patients with diabetes as compared to controls. Similar results were obtained by previous studies.[6,13,14] Fibrinogen has an independent effect on cardiovascular mortality suggesting that both endothelial dysfunction and chronic inflammation are involved in the excess cardiovascular mortality of type 2 diabetic patients.[5]

Plasma fibrinogen levels showed an increasing trend with age. A study done by Bruno et al.[6] reported positive association of fibrinogen levels with age. No significant association was found between fibrinogen and sex. Study done by Jain et al.[13] also did not find any association between fibrinogen and sex.

In our study, fibrinogen level showed significant association with body mass index. Similarly, association between body mass index and fibrinogen was found in previous studies.[13,15]

In this study, mean fibrinogen level was high in patients with poor glycemic control. The correlation between glycemic control

**Table 1**
Clinical and biological parameters of diabetic patients and controls.

| | Diabetic patients | Controls | *P* value | Significance |
|---|---|---|---|---|
| Subjects | 60 | 30 | – | – |
| Mean age (years) | 56.5 ± 9.33 | 56.2 ± 9.76 | 0.87 | Not significant |
| Sex (M/F) | 30/30 | 15/15 | – | – |
| Body mass index (kg/m$^2$) | 27.46 ± 3.68 | 27.20 ± 3.92 | 0.73 | Not significant |
| Fibrinogen (mg/dl) | 380.03 ± 101.07 | 244.43 ± 61.27 | <0.0001 | Significant |