

Research Article

Serum fibrinogen level in type 2 diabetes mellitus patients

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ABSTRACT

Background: Diabetes mellitus is the most common metabolic disorder characterized by metabolic abnormalities and long term complications. The chronic complications of diabetes mellitus affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. The aim of the study is to estimate the serum fibrinogen level in patients of Type 2 diabetes and correlate it with parameters like glycemic control (HbA1C), duration of diabetes mellitus, complications and pharmacotherapy.

Methods: The study was conducted at the medicine department of J. A. Group of Hospital & G. R. Medical College, Gwalior, included patients of type-2 diabetes mellitus with or without microvascular complications between the ages of 25-85 years of either sex. Total 60 patients were selected randomly divided in two groups: Group A (n=34) was type-2 diabetes mellitus with microvascular complication, Group B (n=26) was type-2 diabetes mellitus without microvascular complication and Group C (n=28) was non diabetic healthy control. Patient's history, clinical examination, routine blood tests, serum fibrinogen level and fundus examination were carried out. Serum fibrinogen was measured by Clauss method.

Results: Maximum number of patients in study was between 40-60 years' age group. Microvascular complication in Group A were nephropathy (n=17), retinopathy (n=13) and neuropathy (n=4). Serum fibrinogen level in patient with microvascular complications, without microvascular complications and in non-diabetic controls were 515 ± 138.7 , 437 ± 137 and 308 ± 52.65 respectively. Serum fibrinogen level was higher in overweight patients as compared to normal weight patient in all groups. Serum fibrinogen level in different albuminuria groups (<30mg/l, 30-300mg/l, >300mg/l) were 439.7 ± 135.15 , 525.7 ± 145.4 , 545.7 ± 112.2 respectively. Mean fibrinogen level was 541.1 ± 121.7 in diabetics with total cholesterol >200. Serum fibrinogen level in patients with HbA1C >12% among both group A & B was 567.5 ± 173.4 and 538.6 ± 184.6 respectively. Most of type-2 diabetes mellitus patient have high fasting blood sugar >126 and high PPBS >200 in both group A & B. Mean fibrinogen level in patients taking insulin, oral hypoglycemic agents and in patients who were not taking any treatment was 640.8 ± 126.4 , 449.9 ± 145.7 , 419 ± 72 respectively.

Conclusions: Further larger studies are required studying the serum fibrinogen level in diabetic patients with microvascular complications and effect of interventions done to reduce the fibrinogen levels.

Keywords: Type 2 diabetes mellitus, Microvascular complications, Serum fibrinogen, Nephropathy, Retinopathy, Neuropathy

INTRODUCTION

Diabetes mellitus is a group of metabolic disorder characterized by hyperglycemia resulting from defect in insulin secretion, insulin action or both.¹ The chronic complications of diabetes mellitus affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be vascular (Microvascular and macrovascular) and non-vascular (foot ulcer, infections and dermatological manifestations).² Microvascular complications include diabetic nephropathy including micro albuminuria, diabetic retinopathy and diabetic neuropathy.³

Clinical evidence of nephropathy is the appearance of low but abnormal level of albumin in the urine as “micro albuminuria” in which urinary albumin excretion rate (UAER) is between 20 µg/min to 200 µg/min or total albumin per day between 30 mg to 300 mg. Albumin excretion in normal healthy individuals ranges from 1.5 to 20 µg/min with geometric mean in the range of 6.5 µg/min which is termed as normoalbuminuria.³ Diabetic retinopathy is a common complication of diabetes affecting the blood vessels in retina if untreated it may lead to blindness, if diagnosed and treated promptly, blindness is usually preventable.⁴ Diabetic neuropathy occurs by microvascular injury involving small blood vessels that supply nerves in addition to macrovascular conditions that can culminate in diabetic neuropathy.

Plasma fibrinogen is an important component of the coagulation cascade as well as a major determinant of blood viscosity and blood flow. Increasing evidence from epidemiological studies suggest that elevated plasma fibrinogen levels are associated with an increased risk of cardiovascular disorders including ischemic heart disease, stroke and others like thromboembolism.^{5,6} It has been reported that high fibrinogen concentration enhances the risk of cardiovascular disease in diabetic patients.⁷⁻⁹ Increased level of fibrinogen is a recognized risk factor for macrovascular disease through its variety of mechanisms including increased blood viscosity, increased size of fibrin clots, increased tissue deposition, stimulation of atherosclerosis and vascular thickening.¹⁰ Insulin acutely increases fibrinogen production in an individual with type-2 diabetes but not in individual without diabetes. There is significant correlation between fibrinogen level and duration of diabetes, FBS, PPBS & HbA1C.¹¹

The relation between specific and nonspecific determinants of mortality in diabetes is dominated by the incremental risk of microvascular complications in the form diabetic nephropathy, diabetic retinopathy and neuropathy and also changes like dermopathy and

myopathy etc. The exact pathogenesis of microvascular complications in diabetes mellitus (DM) is unknown. Oxidative stress, activated renin-angiotensin system (RAS), hyperglycemia, advanced glycosylation end-products (AGE) and oxidized low-density lipoproteins are factor contributing to initiation and progression of endothelial inflammation, ultimately leading to diabetic vascular complications. Diabetes is associated with a hypercoagulable state, possibly related to hyperglycemia.

The aim of the present study was to correlate the association of serum fibrinogen level with different clinical parameters and complication of diabetes like glycemic control (HbA1C), duration of diabetes, microvascular complications and therapy with oral hypoglycemic agent or insulin.

METHODS

Study was conducted at J.A. Group of Hospital & G. R. Medical College, Gwalior in patients who attended medicine OPD. Patients of type 2 diabetes mellitus with or without microvascular complications were enrolled after taking written informed consent. Patients with coronary artery disease, cardiomyopathy, malignancy, pregnancy, cerebrovascular accident, patient with chronic liver dysfunction, chronic alcoholics, other causes of albuminuria which includes acute febrile illness, excessive exercise, orthostatic proteinuria, cardiac failure were excluded from the study.

Total 60 patients were enrolled, out of them 34 patients were type 2 diabetes with microvascular complications (Group A), 26 patients were type-2 diabetes without microvascular complications (Group B) and 28 patients were non diabetic healthy controls (Group C).

Each patient was subjected to detailed history and clinical examination including age of patient, sex, duration of diabetes, existence of symptoms like numbness, hyperesthesia, any visual problem, history of taking any anti-diabetic medication & complete examination including fundus, CNS examination. All routine investigations were done at department of pathology & biochemistry, G.R. Medical College, Gwalior. Serum fibrinogen level was measured by modification of claus method.¹²

Analysis was done using software EPICAL and EPIMAX. Mean, standard deviation and p value were measured in all statics by student t test and ANOVA t test. P value <0.05 was considered significant.

RESULT

Table 1: Distribution of patients according to microvascular complications in Type 2 Diabetes mellitus (Group A, n=34)

Complication	Alone	Combination with other microvascular complication	Total
Nephropathy	8 (23.5%)	15 (44.11%)	23 (67.64%)
Retinopathy	6 (17.64%)	15 (44.11%)	21 (61.76%)
Neuropathy	2 (5.8%)	12 (35.29%)	14 (41.11%)

Table 2: Mean fibrinogen level in different groups

	Group A (n=34)	Group B (n=26)	Group C (n=28)	P value
Fibrinogen level (Mean±SD)	515±138.7	437±137	308.53±52.65	0.002

Table 3: Relationship between mean fibrinogen level with albumin excretion rate (mg/L)

	n = No. of patients	Fibrinogen level (Mean±SD)	P value
<30 (Normal Albuminuria)	37	439.7±135.5	0.04
30 – 300 (Microalbuminuria)	16	525.7±145.4	
>300 (Macroalbuminuria)	7	545.7±112.2	

Table 4: Relationship of serum fibrinogen with glycosylated haemoglobin

HbA1C (%)	Group A (n=34)			Group B (n=26)		
	n=No.	Fibrinogen (Mean±SD)	P value	n=No.	Fibrinogen (Mean±SD)	P value
6.5-9	8	413.4±124.8	0.05	7	372.8±62.49	0.04
9-12	14	514±99		12	409.33±109.6	
>12	12	567.5±173.4		7	538.6±184.6	

Table 5: Relationship of serum fibrinogen level with hypoglycemic agent in all diabetic patients

	n = No. of patients	Fibrinogen level (Mean±SD)	P value
No Hypoglycemic agent	7	419±72	0.01
On Oral Hypoglycemic agent	44	449.9±145.7	
On Insulin	9	640.8±126.4	

Out of total 60 patients of type 2 diabetes mellitus, 26 patients were with microvascular complications. Maximum number of patients were in the age group between 40-60 years in group A, B and C (healthy controls) which were 23 (67.64%), 12 (46.15%) and 14 (50%) respectively. Mean age was 53±13, 48±15 and 49±12 in group A, B and C respectively. The distribution of patients according to various microvascular complications in type-2 diabetes mellitus patients is shown in Table 1. Microvascular complication (nephropathy, retinopathy & neuropathy) were progressively increased with duration of diabetes. In more than 10 years duration of diabetes group 100% patients had nephropathy & retinopathy and 75% patient had neuropathy. Mean duration of diabetes was 5.5±3.4 years.

Serum fibrinogen level was elevated in both groups A and B compared to group C in which serum fibrinogen level was normal (Table 2). Among group A serum

fibrinogen level was more elevated compare to group B which is statistically significant (p value <0.05). Serum fibrinogen level was high in overweight patients than normal weight patients which is (564±129, 433±139, p value = 0.01) and (492.2±166.7, 416.9±126.7, p value = 0.002) in groups A and B.

Mean fibrinogen level was (381.7±118.1, 541.1±121.7) in type-2 diabetes mellitus patient with total cholesterol (<200, >200) group. P value for relationship of total cholesterol with serum fibrinogen level was 0.05 whereas P value for relationship of TG, LDL & HDL with serum fibrinogen level were 0.08, 0.96 & 0.31 respectively.

Most of the patients in both the groups has high HbA1c (9 – 12%) and serum fibrinogen level was elevated in patients with high HbA1c (Table 4). Most of type-2 diabetes mellitus patients had poor diabetic control and have high fasting blood sugar (>126) and high PPBS (>200) in both group A and B. No significant association

found between serum fibrinogen level and FBS & PPBS. Serum fibrinogen level was higher in patients on insulin as compared to patients on oral antidiabetics.

DISCUSSION

Serum fibrinogen is an inflammatory marker and has an important role in pathogenesis of inflammation, atherosclerosis, thrombogenesis and development of vascular complications in type-2 diabetes mellitus patients.

In present study, patients were selected from 27 to 85 years of age. Majority of patients were in 40-60 years age group. Mean age for group A, B and C was 53 ± 13 , 48 ± 15 and 49 ± 12 years respectively which was similar to study carried out by Demirci et al, where mean age was 59 ± 10 and 60.88 ± 8.96 years in type-2 diabetes mellitus patient with or without microvascular complications.¹³

In current study, most common microvascular complication found was nephropathy in 23 patients (67.64%) followed by retinopathy in 21 patients (61.76%) and neuropathy in 14 patients (41.17%). Similar findings were found by Madan et al in their study that nephropathy was most common complication than retinopathy and neuropathy.¹⁴

In present study, microvascular complications increased with duration of diabetes. Nephropathy was found in 53.8%, 70.55% and 100% patients with duration of diabetes <5 years, 5-10 years and >10 years group respectively. Retinopathy was increased with duration of diabetes found in 53.8%, 58.8% and 100% patients with duration of diabetes <5 years, 5-10 years and >10 years group respectively. Neuropathy was also increased with duration of diabetes found in 32.7%, 41.12% and 75% patients with duration of diabetes <5 years, 5-10 years and >10 years group respectively. Similar type of finding was also found by Kuzhuppilly et al, who reported that 80.3% patients with diabetic retinopathy has duration of diabetes more than 5 years.¹⁵

In present study, serum fibrinogen level was significantly higher in all diabetic patients compared to non-diabetic control. Mean serum fibrinogen level in group A was 515 ± 138.7 and group B was 437 ± 137 , which was significantly higher than group C in which mean fibrinogen level was 308.53 ± 52.65 . (p value <0.003). Similar results were found by Kalfe et al, where they reported high mean fibrinogen level (341 ± 70) in diabetic patients compared to healthy non diabetic control (216 ± 43).¹⁶

The mean fibrinogen level increased with BMI and in group A between overweight and normal healthy controls was 564 ± 129 and 433 ± 139 respectively (p value = 0.01). Mean fibrinogen level in group B and C was also higher in overweight as compared to normal weight patients.

Our findings are similar to Kalfe et al, who reported an association between fibrinogen level and BMI.¹⁶

A significant association between total cholesterol and fibrinogen has been reported but no significant association exists between LDL, TG and fibrinogen levels.¹⁶ In current study, mean fibrinogen level was higher in patients with total cholesterol >200 mg/dl (541.1 ± 121.7) as compared to patients with total cholesterol <200 (381.7 ± 118.1) but no significant association of fibrinogen with TG, HDL and LDL was found. Present study also shows significant association between serum fibrinogen level and urine albumin excretion rate, which is similar to the findings of Burno et al.¹⁷

Most of type-2 diabetes mellitus patients had poor diabetic control and have high fasting blood sugar (>126) and high PPBS (>200) in groups A and B. No significant association was found between serum fibrinogen level and FBS & PPBS. Similar study was done by Kuzhuppilly et al, who found that there is significant correlation between plasma fibrinogen level and fasting glucose but did not find any correlation with PPBS.¹⁵

Serum fibrinogen level in patients with HbA1C >12% in groups A and B was 567.5 ± 173.4 and 538.6 ± 184.6 respectively. Serum fibrinogen level progressively increased with HbA1C level and positively correlation was seen between fibrinogen level and HbA1C (p value <0.05). Similarly, in study of plasma fibrinogen level and cardiovascular risk factor in Japanese school children, Fujii et al found a significant association between plasma fibrinogen and HbA1C level.¹⁸

The patients on insulin therapy had higher serum fibrinogen levels as compared to the patients on oral hypoglycemic. Insulin cause intensive glycemic control lead to potential benefit effects but a possible adverse effect in increase fibrinogen level. Similar study was done by Emanuele et al¹⁹ which found that intensive insulin therapy beneficially reduced serum TG, total cholesterol and HDL cholesterol but it causes transient elevation in plasma fibrinogen level, a possible thrombogenic effect.

CONCLUSIONS

To conclude serum fibrinogen level was found to be higher in type 2 diabetic patients as compared to non-diabetic controls and it was further increased in patients with microvascular complications. Serum fibrinogen level was higher in patients having uncontrolled diabetes, high cholesterol and on insulin therapy. However, the limitation of our study is the smaller study population. Further larger studies are required studying the serum fibrinogen level in diabetic patients with microvascular complications and effect of interventions done to reduce the fibrinogen levels.

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