

Original Research Article

Correlation of Fibrinogen and HsCRP with Microvascular Complications of Type 2 Diabetes Mellitus

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ABSTRACT

Background: Fibrinogen a plasma protein is the initiating factor in coagulation. A state of hyperfibrinogenemia is found in diabetes, which is an independent risk factor for various vascular complications of diabetes mellitus.

Aims and objectives:

1. To evaluate plasma fibrinogen & HsCRP levels and correlate them with microvascular complications of Type 2 Diabetes Mellitus (T2DM).
2. Correlation of fibrinogen with Albumin Excretion Rate(AER) and HbA1c in T2DM with age & sex matched controls

Methods: In the present study, fibrinogen & HsCRP levels were estimated in 60 T2DM and examined for their vascular complications and 30 matched controls were also studied. Fibrinogen & HsCRP were correlated with microvascular complications of diabetes. Other risk factors were also correlated.

Results: 85% of the cases had uncontrolled diabetes. Diabetics had a higher mean fibrinogen 386.05 ± 147.17 mg/dl when compared to controls 268 ± 49.92 mg/dl. HsCRP levels were also increased in diabetics ($2.34 + 1.62$ mg/dl) when compared to controls (0.6 ± 0.2 mg/dl).

Fibrinogen & HsCRP levels was significantly correlated with microvascular complications ($p < 0.0001$). There was good correlation of fibrinogen & HsCRP with microalbuminuria ($p < 0.0001$), duration and control of diabetes.

Conclusion: Fibrinogen contributes to procoagulant state observed in diabetes, which leads to vascular complications. Microalbuminuria is the best predictor of fibrinogen levels in T2DM. Fibrinogen & HsCRP should be added to the list of screening tests for diabetics to identify high risk subjects.

Key words: Type 2 Diabetes mellitus, plasma fibrinogen, HsCRP, Urine Albumin Excretion Rate, Microalbuminuria.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder of hyperglycemia. [1] Chronic hyperglycemia contributes for initiation and progression of micro and macrovascular complications in diabetics. [2] Diabetic complications are the leading causes of morbidity & mortality. [3]

Fibrinogen is a plasma protein - factor I in coagulation cascade. A state of hyperfibrinogenemia is found in diabetic patients. Fibrinogen is an independent risk factor for various vascular complications of diabetes mellitus. However, the mechanisms leading to increased fibrinogen concentration in type 2 diabetic patients

remain unknown. Clinical stages of vascular disease are indeed per se, associated with increased plasma fibrinogen in nondiabetic patients, [4,5] whereas established macrovascular complications are, in turn, related to higher fibrinogen concentration in a mixed type 1 and type 2 diabetic populations. [6] Microalbuminuria also represents a sensitive marker of cardiovascular disease [7] that is associated with hyperfibrinogenemia in type 2 diabetes. [8]

High fibrinogen concentration and turnover observed in advanced nephrotic nondiabetic patients suggest a direct independent relationship between enhanced renal albumin excretion and increased fibrinogen metabolism. [9]

C-reactive protein (CRP), an acute phase reactant, has long been considered as a classic marker for inflammation. As atherosclerosis involves inflammation of the vascular endothelium, CRP levels tend to be raised. [10] Several prospective clinical case control studies in Europeans have identified CRP as a strong, independent risk factor for coronary artery disease (CAD). [11] With the advent of high sensitive HsCRP assays, this risk factor is gaining importance in the field of CAD and atherosclerosis. Basic research studies have revealed that inflammatory markers are high among subjects with insulin resistance and diabetes. [12] Inflammation is considered to be a part of insulin resistance syndrome and this to some extent explains the high risk for CAD among diabetic subjects. [13]

Microalbuminuria is most commonly associated with other microvascular complications of diabetes namely retinopathy, neuropathy & nephropathy. So microalbuminuria may be a marker for widespread microvascular damage in a patient of diabetes mellitus.

This study was undertaken to correlate fibrinogen and HsCRP with diabetic state and its microvascular complications.

Objectives of the Study

1. Estimation of Fibrinogen and HsCRP levels in type 2 diabetes mellitus (T2DM) & controls. It is correlated with microvascular complications of T2DM.
2. Correlate the association of fibrinogen level with various risk factors -HbA1c, duration of DM and Albumin excretion rate (AER).

MATERIALS AND METHODS

60 patients presenting with T2DM were evaluated clinically for complications with a predetermined proforma and investigated for plasma fibrinogen levels, HbA1c levels, HsCRP, Urine for AER and routine investigations.

Cases were selected as patients with T2DM, either recently detected based on American Diabetic association (ADA) criteria or patients who were on antidiabetic medication admitted to the department of medicine at rural tertiary care centre during the study period.

30 normal controls were selected who were age, sex and Body Mass Index (BMI) matched to the cases and studied for plasma fibrinogen & HsCRP levels.

Patients who gave written consent for the study and fulfilled the inclusion and exclusion criteria were included in this study. The study was approved by the institutional ethical committee.

Inclusion criteria

Patients with type 2 diabetes mellitus more than 40 years of age.

Exclusion criteria

1. Pregnant Diabetics
2. Patients with type 1 diabetes mellitus
3. Chronic Kidney Disease (CKD)/End Stage Renal Disease (ESRD) cases
4. Patients presenting with Urinary Tract Infections (UTI)/ primary renal disorders
5. Patients with hypertension
6. Chronic liver diseases
7. Patients with Acute inflammatory conditions.

Statistical analysis

All the data were analysed by using excel package. Univariate analysis was

carried out to study the differences in mean level among the factors. Students t test and correlation analysis were done to find out significant differences between the two groups. For more than 2 groups, analysis of variance (ANNOVA) was adopted. All tests were considered significant at $p < 0.05$ level. SPSS version 15 for windows was the

statistical package used for all statistical analysis of data collected in the course of the study.

RESULTS

Baseline characters of cases and controls are shown in table 1.

Table 1: Showing baseline characters of cases and controls.

	Cases (60)	Controls (30)	p Value
Age (Years)	53.2 ± 11.15years	53.56 ± 9.87	0.3
Sex (M:F)	34: 26 (56.67:43.33%)	17: 13 (56.67:43.33%)	
BMI Kg/m ²	22.9 ± 4.7	23 ± 4.8	0.3
T. cholesterol mg/dl	189.33 ± 47.8	141.43 ± 36.2	0.02
LDL mg/dl	103.65 ± 40.9	72.56 ± 24.3	0.03
HDL mg/dl	43.95 ± 11.7	43.4 ± 6.2	0.82
Triglycerides (mg/dl)	213.95 ± 51.2	118.1 ± 35.9	0.01
S. Creatinine mg/dl	0.98 ± 0.26	0.84 ± 0.2	0.12
HbA1c	8.88 ± 2.2	5.1 ± 0.6	< 0.0001

The duration of diabetes in maximum number cases in this study was between 1 to 5 years (41.67%) with a mean duration of 3.12 years. 19 cases were recently detected (31.9%) to have diabetes and the longest duration was 15 years.

Euglycemia was seen 15% of the cases and remaining 85% cases had uncontrolled hyperglycemia. It was unsatisfactory in 30% of cases with HbA1c $\geq 10\%$ and 55% had HbA1c between 6.6 to 10%.

Diabetics had dyslipidemia with higher mean total cholesterol (189.33 mg/dl), triglyceride (213.95 mg/dl) and Low Density Lipoprotein (LDL) (103.65 mg/dl) when compared to non-diabetics. There was a statistically significant correlation between lipid profile in controls and diabetics ($p < 0.05$). There was no difference in High Density Lipoprotein (HDL) levels between cases and controls in the present study.

85% of cases had hyperglycemia. Hence there is a higher chance of dyslipidemia. In the present study, 40% of cases were recently detected as diabetes, and majority of them (61.66%) had normal BMI, hence, lipid abnormalities were not significantly changed in this study.

The mean fibrinogen was 268 ± 49.92 mg/dl and HsCRP was 2.34 ± 1.62 mg/dl, significantly higher in diabetics when compared to controls (Table 2).

Table 2: Showing mean fibrinogen an HsCRP in cases and controls

	Cases (60)	Controls (30)	p Value
Mean Fibrinogen (mg/dl)	386.1 ± 147.2	268 ± 49.9	< 0.0001
Mean HsCRP (mg/dl)	2.34 ± 1.6	0.6 ± 0.2	< 0.0001

Fibrinogen & HsCRP were directly related to duration & control of diabetes (tables 3 & 4).

Table 3: Showing plasma fibrinogen and HsCRP level in relation to duration of diabetes

Duration	N	Plasma Fibrinogen (mg/dl)	HsCRP Level (mg/dl)
Newly Detected	19	289.21 ± 60.5	0.84 ± 0.46
<1 Year	5	396.6 ± 90.4	1.15 ± 0.37
1 - 5 Years	25	416.2 ± 155.3	3.64 ± 1.35
> 5 Years	11	480 ± 137.5	5.14 ± 2.11
p Value	-	0.0008	< 0.0001

Table 4: Showing plasma fibrinogen and HsCRP levels in different HbA1c groups

HbA1c	N	Plasma Fibrinogen (mg/dl)	HsCRP Level (mg/dl)
≤ 6.5 %	9	353.67 ± 57.45	1.93 ± 1.43
6.6 % - 10 %	33	366.45 ± 35.42	2.85 ± 1.68
> 10 %	18	438.17 ± 57.4	4.9 ± 4.02
p Value	-	< 0.0001	0.008

Table 5: Showing plasma fibrinogen and HsCRP level in relation to Urine Albumin Excretion Rate

Urine Albumin Excretion	N	Plasma Fibrinogen (mg/dl)	HsCRP (mg/dl)
<30mg/d	40	306.9 ± 72.4	2.14 ± 1.4
30-300mg/d	18	533.83 ± 130.3	4.29 ± 3.7
>300mg/d	2	639 ± 111.7	11.24 ± 8.9
p Value	-	< 0.0001	< 0.0001

Diabetics with increased urine albumin excretion rate had a higher mean fibrinogen and HsCRP levels which were highly significant statistically. High fibrinogen concentrations observed in advanced nephrotic diabetic patients suggest a direct independent relationship between enhanced renal albumin excretion and increased fibrinogen metabolism (Table 5). Similarly, HsCRP levels also correlated well with microvascular complications.

Lipid levels in diabetics, when compared to controls, were significantly higher in respect to total cholesterol, triglycerides & LDL cholesterol. But the

values were not correlated with fibrinogen levels. Hence, there was no statistically significant correlation between lipid profile and fibrinogen levels. Poor nutritional status in rural population and less number of obese individuals in the study population may be the reason for this non-correlation of fibrinogen levels with lipid values.

There was statistically very good correlation of plasma fibrinogen levels with all microvascular complications, suggesting that hyperfibrinogenemia leads to increased vascular complications of type 2 diabetes mellitus (Table 6). Similar results were seen in respect to HsCRP values also.

Table 6: Showing correlation of plasma fibrinogen and HsCRP levels with microvascular complications.

Complication	Microvascular complications		Diabetic Retinopathy		Diabetic Nephropathy		Peripheral Neuropathy	
	Present (27)	Absent (33)	Present (14)	Absent (46)	Present (20)	Absent (40)	Present (19)	Absent (41)
Fibrinogen (mg/dl)	500.92 ± 137.2	292.06 ± 66.1	526 ± 125.37	343.45 ± 126.1	544.3 ± 130.02	306.9 ± 72.4	497.1 ± 132.6	334 ± 124.2
p Value	< 0.0001		< 0.0001		< 0.0001		< 0.0001	
HsCRP (mg/dl)	4.54 ± 3.42	2.35 ± 1.46	3.97 ± 2.27	2.56 ± 2.12	5.06 ± 4.21	2.14 ± 1.41	4.06 ± 3.17	1.96 ± 1.37
p Value	0.02		0.03		0.006		0.01	

Hypercoagulability as evidence by increased fibrinogen levels contribute to procoagulant state observed in diabetes. HsCRP is considered to be chronic marker of arterial wall inflammation, preclinical atherosclerosis and systemic endothelial dysfunction. Endothelial dysfunction, subclinical inflammation and impaired fibrinolysis might contribute to the progression of microvascular as well as to the macrovascular complications, in patients with type 2 diabetes mellitus.

DISCUSSION

The present study is a prospective case control hospital based study to correlate fibrinogen levels and microvascular complications of T2DM. The association of fibrinogen and HsCRP levels with urine albumin excretion rate, duration

and glycaemic control in type 2 diabetes, was studied.

1) Fibrinogen

T2DM cases had higher fibrinogen levels. In all the studies - Ritu Madan et al, [14] R. Barazzoni et al, [15] Anuja J. et al [16] including the present study also has hyperfibrinogenemia. The increase was statistically significant when compared to controls except in the study done by Uma M Iyer and Pallavi Desai [17] (p > 0.5), where the correlation was not significant as they had cases with mild diabetes and normal BMI (Table 7).

2) HsCRP

HsCRP values were significantly increased in diabetics when compared to controls (p < 0.0001). Even other studies - Safiullah Amanullah et al, [18] who studied a large population in Chennai urban rural area, M.S. Roopakala et al [19] demonstrated

that HsCRP has a strong association with diabetes mellitus. Uma M Iyer and Pallavi Desai [17] in their study found that HsCRP levels (1.70 ± 1.65) were higher in diabetics when compared to HsCRP levels (1.16 ± 1.02) in non-diabetics but this difference was not statistically significant, as the cases were mildly diabetics.

3) Urine Albumin Excretion Rate And Fibrinogen

There was positive association between urinary albumin excretion rate and

plasma fibrinogen level in diabetics (Table 8).

Similar results were obtained in studies cited above and also by Anuja J. et al, [16] Gomes MB et al, [22] Festa et al, [23] Knobl Pet al, [24] Mattock MB et al [25] and Tkac I et al. [26]

High fibrinogen concentrations observed in advanced nephrotic diabetic patients suggest a direct independent relationship between enhanced renal albumin excretion and increased fibrinogen metabolism.

Table 7: Fibrinogen levels in different studies:

Authors/Study	Study Population (cases + controls)	Mean fibrinogen Cases (mg/dl)	Mean Fibrinogen Controls (mg/dl)	P Value
Ritu Madan et al [14]	60 + 30	252.75 ± 40.23	227.5 ± 22.8	< 0.05
R. BARAZZONI et al [15]	6 + 7	304 ± 31	210 ± 12	< 0.05
Anuja J. et al [16]	50 + 10	730 ± 587	406 ± 250	< 0.05
Uma M Iyer and Pallavi Desai [17]	27 + 30	242.22 ± 40.36	296.20 ± 30.57	> 0.05
Present Study	60 + 30	386.05 ± 147.2	268 ± 49.9	< 0.0001

Table 8: Fibrinogen level in relation to Urine Albumin Excretion Rate

Authors/Study	Fibrinogen Levels (mg/dl)			p value
	UAE <30 mg/day	UAE 30-300 mg/day	UAE > 300 mg/day	
Bruno G et al [20]	352 ± 3	368 ± 4	377 ± 6	< 0.05
Michaella Dalla Vestra et al [21]	310	340	510	< 0.05
Present study	306.9 ± 72.41	533.83 ± 130.35	639 ± 111.72	< 0.0001

4) Duration Of Diabetes And Fibrinogen

Long standing diabetes is associated with hyperglycemia leading to increased production of fibrinogen. G Bruno et al [20] demonstrated that plasma fibrinogen was significantly higher in relation to duration of diabetes. The present study also showed similar results.

5) Association Of Fibrinogen With HbA1c (Glycemic Control)

Hyperfibrinogenemia is an expression of poor glycaemic control. Fibrin-o-peptide A (a peptide that is released from fibrinogen when it is transformed into fibrin) is positively related to blood glucose. Hyperfibrinogenemia is one way by which hyperglycemia activates coagulation.

Anuja J. et al [16] ($r = 0.99$) and G Bruno et al [20] ($p < 0.001$), showed that fibrinogen level was positively associated with HbA1c value. The present study also showed that fibrinogen level was higher (438.17 ± 57.42) in poorly controlled diabetes HbA1c > 10% which was

statistically significant ($p < 0.0001$). There was positive correlation of fibrinogen with level of blood glucose.

6) Lipid Profile And Fibrinogen

There is a positive correlation between cholesterol, triglycerides, and LDL and a negative correlation between HDL, with fibrinogen. Similar results were observed in a meta-analysis by Ernst et al. [27]

Uma M Iyer and Pallavi Desai [17] in their study demonstrated that fibrinogen levels remained unaltered in relation to lipid profile. Even in the present study also fibrinogen levels were unaltered with respect to lipid profile. Poor nutritional status in rural population and less number of obese individuals in the study population may be the reason for this non-correlation of Fibrinogen levels with lipid values.

7) Correlation Of Plasma Fibrinogen And HsCRP With Microvascular Complications Of Type 2 Diabetes Mellitus

There was a positive correlation of plasma Fibrinogen & HsCRP levels with complications of DM.

Acang and Jalil [28] observed that there were significantly higher fibrinogen levels in diabetic patients, especially in patients with long-term diabetes with chronic complications. Present study also has positive correlation of Fibrinogen & HsCRP with microvascular complications in DM.

Demirci, Huseyin et al [29] showed that the plasma fibrinogen levels were significantly higher in patients with retinopathy and/or nephropathy than in patients without these complications but not significantly higher in patients with

neuropathy than in patients without neuropathy.

Francisco Javier Del Cañizo Gómez et al [30] showed that, urine AER levels higher than 12mg/24h ($p = 0.001$) and HsCRP $> 3\text{mg/L}$ ($p = 0.004$) were independent risk factors for development of microvascular complications in patients with T2DM studied.

These findings are similar to most of the previous studies (Table 9) indicating that diabetes is a hypercoagulable state and hyperfibrinogenemia is associated with chronic microvascular complications of diabetes mellitus and elevated HsCRP levels in diabetes indicates low grade inflammation and contribute to pathogenesis of complications of diabetes mellitus.

Table 9: Correlation of mean plasma fibrinogen with microvascular complications in various studies

Study	Mean Plasma Fibrinogen (mg/dl)							
	Microvascular Complications		Diabetic Nephropathy		Diabetic Retinopathy		Diabetic Peripheral Neuropathy	
	Microvascular complications (+)	Microvascular complications (-)	DN (+)	DN (-)	DR (+)	DR (-)	DPN (+)	DPN (-)
Ritu Madan et al [14]	259.37 ± 40.85	239.5 ± 36.37	262.30 ± 43.45	245.44 ± 36.56	253.92 ± 36.43	239.5 ± 36.37	248.5 ± 32.49	253.6 ± 41.84
	p = 0.07		p = 0.1		p = 0.2		p = 0.71	
Neetha Kuzhuppilly I R et al [31]	-	-	-	-	305.61 ± 126.8	247.74 ± 89.02	-	-
	-		-		p = 0.004		-	
Present Study	500.92 ± 137.2	292.06 ± 66.1	544.35 ± 130.02	306.9 ± 72.4	526 ± 125.37	343.45 ± 126.09	497.1 ± 132.6	334.5 ± 124.2
	p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001	

CONCLUSION

- Fibrinogen levels are elevated positively with degree & duration of hyperglycaemia. Good control of Diabetes will reduce fibrinogen levels leading to decreased complications of Diabetes.
- Fibrinogen contributes to procoagulant state observed in diabetes. This contributes to microvascular complications, as has been observed in this study.
- Albuminuria is the best predictor of plasma fibrinogen levels in type 2 diabetic patients since a strong direct significant correlation exists between them.
- HsCRP should be added to the list of screening tests for diabetic subjects.

Secondly, elevated HsCRP levels may also identify high risk subjects who would be “missed” by just measuring cholesterol and triglyceride levels.

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