

Research Article

The Study of Relationship between Plasma Fibrinogen Level and the Macrovascular Complications in Type 2 Diabetes Mellitus patients in a Tertiary Health Care Centre in Eastern India

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Abstract

Introduction: The macrovascular complications in patients of Type 2 Diabetes Mellitus (T2DM) are an expression of the generalized atherosclerotic process affecting the blood vessels of the body. Studies have revealed cardinal role of inflammation in the development of atherosclerosis. Literature review suggests that the level of plasma fibrinogen, an inflammatory marker, is elevated in T2DM and more so in those with the macrovascular complications. Therefore, this study was taken up with the aim to determine the association of plasma fibrinogen level with the macrovascular complications in patients of T2DM.

Methods and materials: This was a prospective observational study undertaken in Tata Main Hospital from November 2020 to October 2022. It included T2DM out-patients and those admitted in the Department of Medicine between the age group of 40 to 80 years. Patient's clinical history and detailed physical examination were noted. Relevant blood tests (including HbA1c, lipid profile) and plasma fibrinogen levels were done. All patients were evaluated for complications of Coronary Artery Disease (CAD), cerebrovascular disease and peripheral vascular disease using appropriate investigations. The statistical association was determined by chi-square (χ^2) and independent sample t-tests where appropriate. The relationship between plasma fibrinogen level and the macrovascular complications was determined using binary logistic regression.

Results: The study involved 180 patients. Their mean age was 58.63 ± 7.177 years with most patients in 51-60 years age group. Male preponderance was seen and the male to female ratio was 1.86:1. While the average duration of T2DM in the study population was 6.744 ± 2.376 years, mean HbA1c level was $8.2 \pm 1.9\%$ (range: 6.2% to 9.8%). The mean Body Mass Index (BMI) was 24.57 ± 2.49 Kg/m², with 61.67 % of cases having BMI of 25-29.9. The mean fibrinogen level in patients was 446.50 ± 28.449 mg/dl (ranged: 358.3 mg/dl to 513.0 mg/d).

Diabetics without complications had mean fibrinogen level of 443.3 ± 28.3 mg/dl while those with complications had level of 469.6 ± 16.8 mg/dl ($P = 0.000$). 43 (23.9%) patients had macrovascular complications. Peripheral vascular disease was observed in 31 (17.2%), cerebrovascular disease in 16 (8.9%) and CAD in 20 (11.1%) patients while hypertension was observed in 68 (37.8%) patients. Fibrinogen level showed a positive relation with age ($R = 0.541$, $P < 0.001$), male gender, BMI ($R = 0.515$, $P = 0.0001$), total cholesterol levels more than 200 mg/dl ($R = 0.365$, $P = 0.0001$) and HbA1c ($R = 0.355$ with $P = 0.0001$). Binomial logistic regression demonstrated significant association between plasma fibrinogen level with macrovascular complications of diabetes (Wald test: 7.482, odds ratio-1.062, $P < 0.01$). Furthermore, the association was found to be independent after adjusting for the confounding factors.

Conclusion: Our study suggests that plasma fibrinogen level may be viewed as an independent risk factor for the development of macrovascular complications in T2DM patients. Hence, in these patients, it can be used as a marker for the prediction of the macrovascular complications.

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Keywords: Diabetes; Mellitus; Serum; Fibrinogen; Macrovascular; Plasma

Abbreviations

T2DM: Type 2 Diabetes Mellitus; BMI: Body Mass Index; CAD: Coronary Artery Disease; T1DM: Type 1 Diabetes Mellitus; PAD: Peripheral Arterial Disease

Introduction

Past twenty years have witnessed a sharp increase in the prevalence of Diabetes Mellitus (DM) worldwide, from an estimated 30 million cases in 1985 to 177 million in 2015, with 90 to 95% patients having T2DM [1,2]. Incidence of T2DM is soaring high due to increasing obesity, aging population, declining levels of physical exercise, sedentary lifestyle and psychosocial stress. By 2030, about 439 million people would have developed diabetes worldwide, according to the current trends [2]. It is now recognized as a global epidemic by the WHO. With India becoming the diabetic capital of the world in 2000, the numbers of diabetic patients are projected to dangerously increase to about 134 million by 2045 from 77 million in 2019, with every fifth diabetic person on the globe being an Indian [3,4]. A national surveillance study by Mohan, et al., reported prevalence of 7.3 % in urban regions and 3.2 % in peri-urban areas of India [5].

The most significant contributors to morbidity, death and disability in patients with T2DM are the macrovascular complications. The major cause of death in an adult diabetic is CAD, which kills nearly three times more diabetics than the non-diabetics [6]. The classic risk factors for macrovascular diseases like smoking, obesity, hypercholesterolemia, family history, physical inactivity, diabetes mellitus and hypertension represent only one-third to one-half of the real risk [7]. It is, hence, crucial to identify additional risk variables, especially the ones that are simple to change or address. Oestrogen insufficiency, lipoprotein(a), plasma fibrinogen, plasminogen-activator inhibitor type 1, Interleukins (IL-6), C- reactive protein, Tumour Necrosis Factor (TNF)-alpha and homocysteine are a few of the factors, whose roles are actively being researched [7].

Fibrinogen, a precursor of fibrin, plays a vital role in the aggregation of platelets and determining blood viscosity [8]. Literature review suggests that fibrinogen may have a role in the formation of atherosclerotic plaques, including the early stages [9]. Thus, increased fibrinogen level in diabetes plays a significant role in the emergence of complications of atherosclerosis in various organs. There is paucity of data and studies on the relation of plasma fibrinogen level with the macrovascular complications of diabetes, especially in Eastern India, hence this study was carried out towards filling this gap.

Aim

1. To detect the plasma fibrinogen level in in patients with T2DM and compare with that of the normal controls
2. To study the association (if any) of plasma fibrinogen level with the macrovascular complications in these patients

Inclusion Criteria

1. Cases of T2DM, both newly diagnosed and those on treatment
2. All patients more than 40 years

Exclusion Criteria

1. Patients with T1DM
2. Any infectious or inflammatory diseases
3. Haematologic disorders and malignancies
4. Thyroid disorders
5. Severe liver insufficiency (transaminases >10 times the upper limit of normal)
6. Renal insufficiency (end-stage renal disease or chronic dialysis treatment)
7. Patients on medications like warfarin, steroids and hormone replacement therapy

Ethical Statement

This study was conducted in accordance with the ethical standards of the Institutional Ethics Committee.

Methodology

This was a prospective, observational study done from 1st November 2020 to 30th October 2022 in the out-patients and in-patients admitted in the Medicine department of Tata Main Hospital, Jamshedpur, which is a 1030-bedded tertiary industrial hospital and caters to a large population from the surrounding rural and urban areas of Jharkhand. This study was sanctioned by the Institutional Ethics Committee. Patients who satisfied the inclusion criteria participated in the study. Data obtained from history, clinical examination and relevant laboratory parameters, was entered in pre-designed study proforma. Hundred healthy, age and sex-matched people who came for routine health check-ups in the out-patient department were randomly selected as controls.

Biochemical Estimation

The fasting biochemical parameters checked in all participants were fasting and postprandial plasma glucose, glycated haemoglobin, complete lipid profile, serum creatinine and plasma fibrinogen.

Fibrinogen Estimation

Blood sample was drawn after 14 hours fast and it was mixed with sodium citrate (3.2%) solution in the ratio of 9:1 and was subjected to centrifugation at 1000 rpm for 15 minutes. Plasma was separated from the tube and was stored in plastic tubes at -20°C. Within 10 days of storage, plasma fibrinogen level was measured by Clauss method as per the prescribed guidelines.

Criteria/Case Definition

1. Diagnosis of T2DM

- Fasting plasma glucose > 126 mg/dl and two hours post prandial plasma glucose more than 200mg/dl [10]
- Known cases of T2DM on/not on medications

2. Hypertension

- Blood Pressure \geq 140/90 mm of Hg measured in sitting posture on at least two or more visits [11]
- Known hypertensive patients on medications or not taking them

3. Obesity

Obesity was defined in terms of the Body Mass Index (BMI), which is the ratio of weight in kilograms and height in (meter)². It was graded into three classes as per the criteria given by the WHO [12].

Criteria for Macrovascular Complications

Cardiovascular Disease (Presence of any two of the three following criteria)

1. History of angina, myocardial infarction and/or congestive heart failure
2. ECG features
 - a. ST - T changes of ischaemic heart disease
 - b. Features of old myocardial infarction
3. Echocardiographic evidence of regional wall motion abnormality (RWMA) with/without decreased ejection fraction

Peripheral Arterial Disease (PAD)

1. History of claudication pain in the lower limbs
2. Duplex ultrasonography showed evidence of PAD

Cerebral Vascular Disease (Stroke) (Presence of one clinical and one radiological criteria)

1. History of transient ischaemic attack (TIA), stroke (recent/past)
2. Clinical examination showing evidence of focal neurological deficit
3. Imaging studies (CT/MRI) showing evidence for stroke

Statistical Analysis

Statistical analysis was carried out with SPSS version 26. The normal distribution of the variables was analyzed. Continuous variables with normal distribution were expressed as mean \pm standard deviation while the quantitative variables were presented

as percentage. The statistical association was determined by chi-square (χ^2) and independent sample t-tests where appropriate. P value of < 0.05 was considered statistically significant. Pearson and spearman correlation coefficient was calculated where applicable. Binary logistic regression was used to find the association between plasma fibrinogen level and macrovascular complications of diabetes.

Results

There were 180 patients in the study. Their mean age was 58.63 ± 7.177 years with the largest age group being 51-60 years (51.1%) as depicted in the Fig. 1. 3.3% of the study population was beyond seventh decade of life. While the youngest patient was 41.4 years, the oldest was 78.2 years. The mean age was 52.43 ± 11.23 years for the control group.

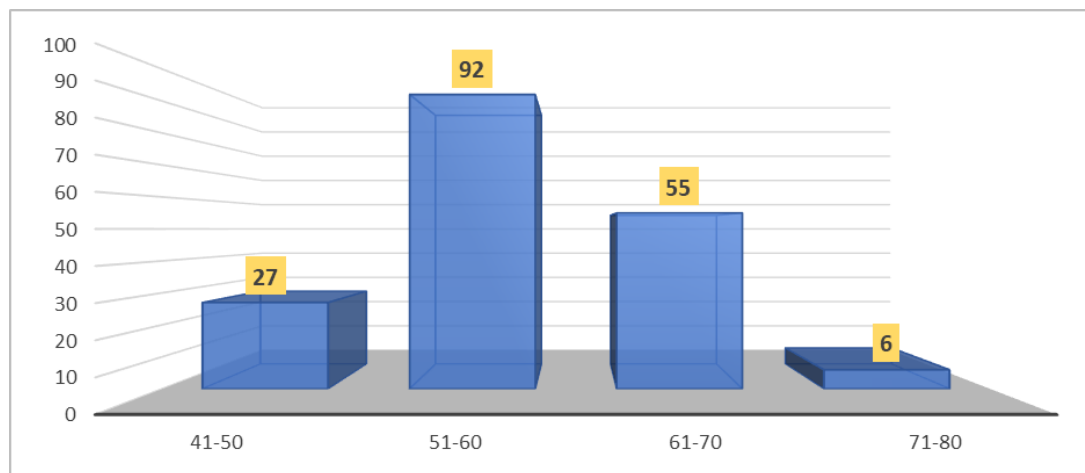


Figure 1: Age distribution in study population (n=180).

There was male preponderance in the study and the observed male to female ratio was 1.86:1. The average weight of the study sample was 65.4 ± 5.117 kg and the mean BMI was 24.57 ± 2.49 Kg/m². 61.67 % of cases had BMI between 25-29.9 (WHO category: pre-obesity), 6.7% of the study group was normal weight while 30 (16.7%) patients had WHO obesity class 1. The distribution of BMI is as shown in the Fig. 2.

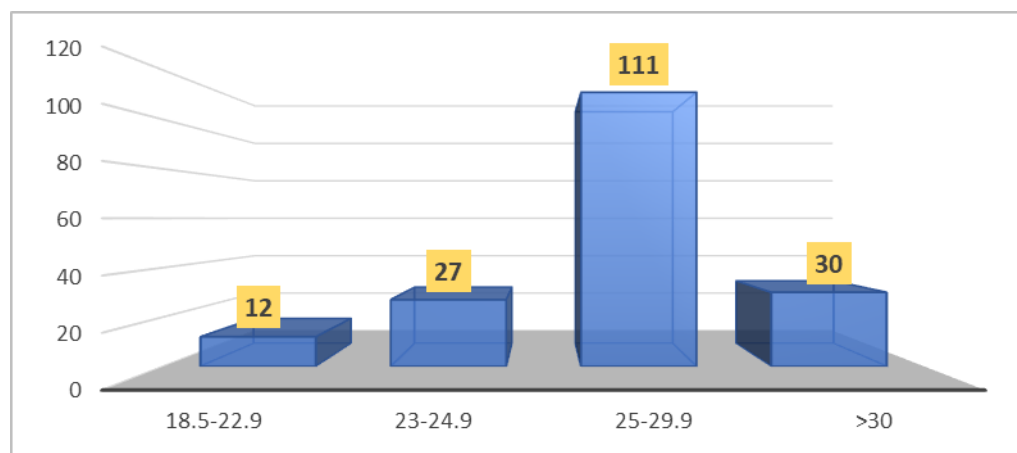


Figure 2: BMI classification of the study population (n=180).

The average duration of diabetes was 6.744 ± 2.376 years (range: 3 to 11 years), with 34% of the patients having DM from 8 to 11 years. The mean HbA1c level was $8.2 \pm 1.9\%$ with the lowest value being 6.2% and highest value was being 9.8%. The mean fibrinogen level in the study group was 446.50 ± 28.45 mg/dl and varied from 358.3 mg/dl to 513.0 mg/dl (Fig. 3) while it was 326.60 ± 33.76 mg/dl in the control group ($t = 30.8$, $P < 0.0001$) (Table 1).

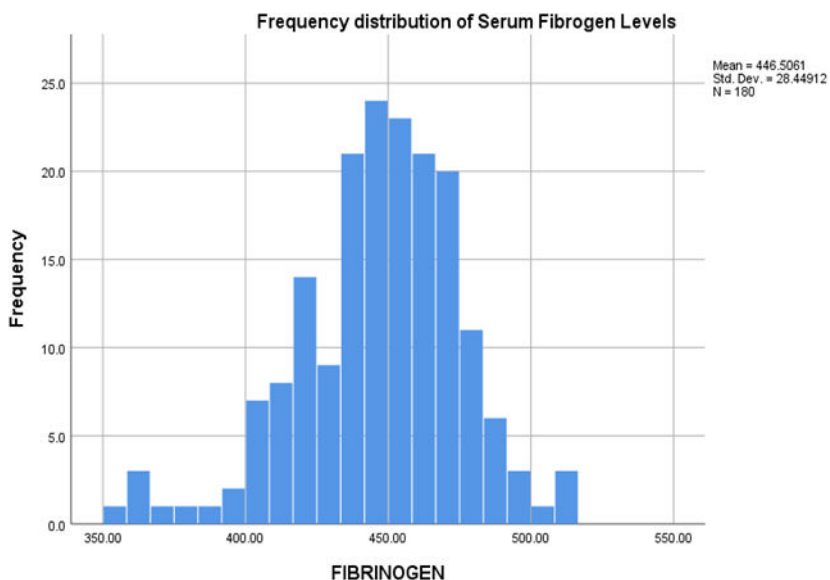


Figure 3: Frequency distribution of plasma fibrinogen level in the study population.

Also, the mean fibrinogen level in Type 2 DM with macrovascular complications was 465.87 ± 71.21 mg/dl, while in those without complications, was 440.43 ± 28.60 mg/dl ($t = 3.4101$, $p=0.0008$) (Table 1).

Group	Plasma Fibrinogen (mg/dl) \pm SD	P-value (vs control)
DM without complications (n = 137)	440.43 ± 28.60	<0.0001
DM with complications (n = 43)	465.87 ± 71.21	<0.0001
DM (total) (n=180)	446.5 ± 28.45	<0.0001
Control (n = 100)	326.60 ± 36.72	

Table 1: Comparison of mean plasma fibrinogen level in diabetic patients with and without complications with that of controls.

43 patients (23.9%) in the study population had macrovascular complications. PVD was observed in 31 patients (17.2%), CVA in 16 patients (8.9%) and CAD in 20 patients (11.1%) while hypertension was observed in 68 (37.8%) patients as shown in Fig. 4.

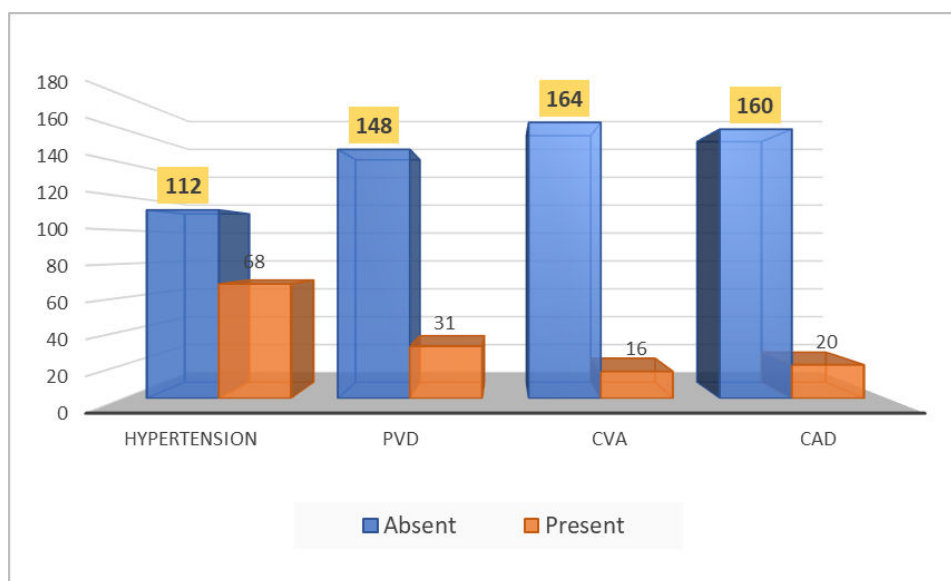


Figure 4: Distribution of complications in the study population (n=180).

Of the various variables, age, BMI, HbA1c, plasma fibrinogen and total cholesterol were observed to be variably significantly associated with the macrovascular complications ($P < 0.01$) while HDL-c level was found to be insignificant (Table 2).

Parameters	Type 2 DM without Complications		Type-2 DM with Macrovascular Complications		P-value
	Mean	Standard Deviation	Mean	Standard Deviation	
Age (years)	57.82	6.99	61.21	7.25	0.007
BMI (kg/m ²)	24.28	2.42	25.49	2.52	0.005
Plasma Fibrinogen (mg/dl)	440.43	28.60	465.87	17.21	0.000
HbA1c (%)	7.65	0.74	8.28	0.75	0.000
Total Cholesterol (mg/dl)	208.63	20.14	219.02	18.30	0.003
HDL (mg/dl)	48.21	3.38	47.79	2.91	0.463

Table 2: Comparison of means of all factors with macrovascular complications.

Deep diving into the role of these factors in the causation of each of the macrovascular complications, age ($p = 0.007$), plasma fibrinogen ($p = 0.001$), total cholesterol ($p = 0.011$) were found to be significantly associated with CVA but BMI, HbA1c and HDL-c were found not to be statistically significant, while in patients with CAD, HbA1c level ($p = 0.000$), plasma fibrinogen ($p = 0.001$) and total cholesterol ($p = 0.007$) were significantly associated with CAD while age, BMI, weight and HDL-c were not found to be significant. Factors like age ($p = 0.000$), plasma fibrinogen ($P = 0.000$), HbA1c ($p = 0.000$) and total cholesterol ($p = 0.014$) were also significantly associated with PVD while BMI and HDL-c were found to be insignificant. Thus, plasma fibrinogen was observed to be statistically associated with all the macrovascular complications. The average plasma fibrinogen levels in patients with diabetes without complications was 443.3 ± 28.3 mg/dl and those with complications was 469.6 ± 16.8 mg/dl respectively ($p = 0.000$).

In order to determine whether fibrinogen level varies with age, correlation analysis was carried out with Pearson formula. Fibrinogen level showed a positive correlation ($R = 0.541$ with $p < 0.001$) with age implying that fibrinogen level increases with advancing age. The mean fibrinogen level in male and female diabetics was 450.95 ± 25 mg/dl and 438.26 ± 32.15 mg/dl respectively. Thus, the level was higher in males than in females and this difference was significant ($p = 0.000$). Plasma fibrinogen level also showed a significant positive correlation ($R = 0.515$ with $p = 0.0001$) with Body Mass Index (BMI). Similarly, fibrinogen level showed a positive correlation (correlation coefficient, $R = 0.355$ with $p = 0.0001$) with HbA1c implying, plasma fibrinogen level increases with rising HbA1c level. Thus, poor glycaemic control was associated with higher fibrinogen level. Also, fibrinogen level was significantly higher in diabetics with total cholesterol level more than 200 mg/dl ($R = 0.365$, $p = 0.0001$). The level was also significantly higher in hypertensive diabetics when compared with the level in those without hypertension (468.36 ± 19.35 vs 433.24 ± 24.68 mg/dl, $p = 0.001$).

In order to remove the effect of confounding factors, a comparison of mean level of plasma fibrinogen between diabetic patients with and without macrovascular complications with three factors namely age, gender and total cholesterol was done. It was found to be significant, thus, establishing that age, gender and total cholesterol did not have confounding effect on the results significantly, as shown in the table below.

		Macrovascular Complications				Significance
		Absent		Present		
		Plasma Fibrinogen		Plasma Fibrinogen		
		Mean	Standard Deviation	Mean	Standard Deviation	
Age Group	<60 years	428.02	24.77	460.79	16.06	<0.05
	> 60 years	449.66	15.77	475.93	19.60	<0.05
Gender	Female	421.71	27.74	463.41	19.76	<0.05
	Male	439.16	20.76	471.24	18.74	<0.05
Total Cholesterol	<200 mg/dl	420.56	26.77	461.54	22.12	<0.05
	> 200 mg/dl	445.04	15.02	469.82	18.60	<0.05

Table 3: Effect of confounding factors on plasma fibrinogen level.

Also, on binomial logistic regression, plasma fibrinogen level was found significantly associated with the macrovascular complications of diabetes (Wald test: 7.482, odds ratio-1.062, $p < 0.01$), in addition to HbA1c levels and duration of diabetes mellitus as shown in Table 4.

	B	S.E.	Wald	df	Sig.	Exp(B)
Age	0.048	0.053	0.823	1	0.364	0.953
Gender	1.692	1.227	1.903	1	0.168	5.431
Weight	0.161	0.133	1.462	1	0.227	0.851
BMI	0.045	0.276	0.027	1	0.870	0.956
HbA1c	1.090	0.526	4.291	1	0.038	2.975
Fibrinogen	0.060	0.022	7.482	1	0.006	1.062
Total cholesterol	0.024	0.024	1.027	1	0.311	1.024
Duration of diabetes	1.547	0.301	26.482	1	0.000	4.696
HDL	0.067	0.108	0.387	1	0.534	0.935
Constant	-37.412	11.597	10.408	1	0.001	0.000

BMI: Body mass index, HDL-c: High density cholesterol, S.E: standard error, df: degrees of freedom, exp(B): Exponential value of B, B: Beta

Table 4: Binomial logistic regression of macrovascular complications with all the variables.

Discussion

Fibrinogen, an inflammatory marker plays a key role in the development of atherosclerosis, thrombogenesis and inflammation, resulting in various macrovascular complications in type-2 diabetes mellitus like CAD, stroke and peripheral vascular disease [13]. Various mechanisms proposed in the development of complications related to high plasma fibrinogen are elevation of plasma viscosity, aggregation of red blood cells, induction of platelet aggregation and activation, stimulation of Vascular Smooth Muscle Cells (VSMC) migration and proliferation, alteration of the integrity of vascular endothelial cells through Intercellular Adhesion Molecule-1 (ICAM-1) and P-selectin and promotion of leucocyte-endothelium interaction [8,9]. It, thus, orchestrates atherogenesis from the stage of plaque formation to the rupture in major vascular beds like the coronaries, peripheral and cerebral vessels leading to the deleterious clinical manifestations.

In our study, the mean age of the population was 58.63 ± 7.177 years. Our observations were similar to those made by Bembde, et al., and Madhu, et al., [14,15]. Mean age of their patients ranged from 53.9 ± 8.9 to 56.4 ± 9.9 years. A high male dominance was noted in the study with male to female ratio of 1.86:1. However, this difference was statistically insignificant. Bembde AS, et al., [14] also reported male dominance with the male to female ratio of 1.3:1, while, studies by Klein, et al., Madhu, et al., and Jain, et al., found higher plasma fibrinogen levels in females, though this difference was insignificant [14-17].

Our study demonstrated positive correlation between plasma fibrinogen levels and BMI. This is in accordance with the studies by Bruno, et al., Klein, et al. and Kafle, et al., [16,18,19]. Moreover, higher plasma fibrinogen level was observed in those with total cholesterol > 200 mg/dl in our study. This was in concurrence with the observations made by Klein, et al. and Jain, et al., [16,17]. Our study did not show significant relationship between HDL-c and fibrinogen level. This was contrary to the studies by Jain, et al., Klein, et al. and Kafle, et al., where higher level of HDL-c was associated with lower fibrinogen level [16,17,19]. Our study showed higher mean fibrinogen level in patients with diabetes complicated with hypertension than in those with diabetes alone. This has also been observed in other studies [20,21]. This implies that hypertension perhaps, has a synergetic effect with diabetes mellitus in the development of complications.

The mean fibrinogen level in diabetics in our study group was 446.50 ± 28.449 mg/dl and was found to be beyond the normal range (200 to 400 mg/dl). Gupta, et al., observed significantly higher plasma fibrinogen level in diabetic than in nondiabetic subset (386.04 ± 132.87 vs 314.38 ± 97.42) in their study [22]. Our study showed a positive correlation with HbA1c level, thus, indicating fibrinogen level increases with uncontrolled diabetic status. Abishek, et al., Ghongade, et al. and Dhawale, et al., also reported similar correlation between HbA1c and mean fibrinogen level [23-25]. The relation between glycaemic control and fibrinogen level may be explained by formation of glycosylated fibrinogen which is resistant to degradation by plasmin. Further, the relative insulin deficiency in type 2 diabetics results in decrease in albumin synthesis with a compensatory increase in fibrinogen synthesis. Thus, a prolonged uncontrolled glycaemic state, results in hyperfibrinogenaemia.

We observed significantly higher level of plasma fibrinogen in diabetic patients with macrovascular complications than those without complications. The results of some of the epidemiological studies support this observation. AtheroGene study included 1,806 stable patients with coronary artery disease followed up for median 3.5 years and found that per Standard Deviation (SD) change of fibrinogen was associated with 1.27-fold higher risk of cardiac death and non-fatal myocardial infarction [26]. Eriksson et al found significantly higher mean plasma fibrinogen value in diabetic women with CAD when compared to those without CAD in Stockholm area [27]. Similarly, Mahmud et al reported that plasma fibrinogen value above 280 mg/dl increased risk of one-year major cardiovascular events after Percutaneous Coronary Intervention (PCI) by 2.65-fold [28]. Sanchez PL et al studied the role of plasma fibrinogen in assessing the prognosis in non-ST-elevation ACS in diabetics and found that patients with elevated plasma fibrinogen had higher mortality during the follow-up [29]. Also, Stec, et al., Kafle, et al., Khan, et al., observed higher plasma fibrinogen values in diabetics with CAD compared to those in non-diabetics and CAD without diabetes [19,30,31]. Maresca et al noted elevated fibrinogen accounts for at least a part of the elevated cardiovascular risk that cannot be explained after taking into consideration the traditional risk factors [32]. Pacilli, et al., showed fibrinogen level independently predicts adverse major cardiovascular events, like non-fatal MI, deaths and stroke in three twenty CAD patients with diabetes during an average follow-up period of 64.2 months [33].

DM is the principal cause of non-traumatic lower limb amputations, with Peripheral Arterial Disease (PAD) being one of the major contributors of its pathology and being an efficient predictor of cardiovascular outcomes. In a Chinese study by Chen et al which included 887 diabetics (type 2), plasma fibrinogen concentration was observed to be an independent risk factor for PAD as measured by duplex ultrasonography [34]. Yet another study by Bosevski, et al., on 62 patients with T2DM and PAD [as defined by Ankle Brachial Index (ABI)], plasma fibrinogen was independently found to influence the progression of atherosclerosis in peripheral arteries [35]. PAD was the commonest macrovascular complication observed in our study followed by CAD and CVD and it was significantly associated with higher plasma fibrinogen levels.

The Framingham study found a significant association between elevated plasma fibrinogen level and risk of stroke in men but not in women. A case-control study by Qizilbash, et al., found a significant association between Transient Ischaemic Attack (TIA) and minor strokes with plasma fibrinogen level [36]. The Copenhagen City Heart Study revealed significantly higher fibrinogen levels in those with ischemic stroke than those without stroke in both diabetic and non-diabetic subjects ($P < 0.0001$) [37]. Similar findings were observed in those with significant carotid artery stenosis ($P < 0.0001$). A 15-year study by Lee et al, involving 3,814 patients, also found Early Neurological Deterioration (END) in diabetic patients with acute ischemic stroke who had significantly elevated plasma fibrinogen level [38].

Thus, the results of our study are in concurrence with those of the earlier published studies, which established that elevated fibrinogen level independently correlates with the risks of macrovascular complications like CAD, cerebrovascular and peripheral arterial disease in patients with T2DM. Fibrinogen level could thus, predict the development of macrovascular complications in these patients. Based on the above results, strict control measures should be initiated in subset of uncontrolled diabetics with high fibrinogen level to prevent the development of the macrovascular complications. Fibrinogen level before starting therapy and during on-going treatment could be a potential marker for the overall efficacy of life-style modifications, therapy and risk reduction.

Some of the study limitations include relatively smaller sample size to determine the prognostic value of plasma fibrinogen. The sample was selected from a single centre in Jharkhand. As there are racial variations in plasma fibrinogen level, we are not sure if our results can be extrapolated to other cultural groups. Larger studies from multiple centres would be required to evaluate our finding. Further, longer duration of follow-up would be required to study the prognostic value of plasma fibrinogen on long-term outcomes.

Conclusion

Plasma fibrinogen level was higher in diabetics, those with poor control (as evidenced by higher HbA1c values), with dyslipidaemias and macrovascular complications. Hence, high plasma fibrinogen level in patients with T2DM should call for more rigorous control of blood sugar, intensive monitoring and early detection of the complications. Fibrinogen level before initializing and after completion of the treatment could serve as a potential measure for overall treatment effectiveness and risk reduction. However, as our study group was small and involved single centre, large-scale studies are required to establish the causative effect of fibrinogen level with the macrovascular complications of T2DM.

Conflict of Interests

The authors declare that they have no conflicts of interest.

Acknowledgement

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Financial Disclosure

None to disclose.

Patient Consent

It was taken from all the patients, is documented in the case records.

Data Availability

Main sheet of the data is available with the corresponding author and will be made available to the editor on demand. Other supporting data is available within the manuscript.

Author's Contribution

Sangita D Kamath (Kamath SD): Conceptualization, data collection, formal analysis, methodology and writing-original draft.

Uppala Sai Prasanna (Sai Prasanna U): Data collection, formal analysis, investigation and methodology.

Saurabh Srivastava (Srivastava S): Writing-review and editing.

Ashok Sunder (Sunder A): Overall supervision, writing-review and editing.

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