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A Study on Plasma Fibrinogen Levels in Type 2 Diabetes Mellitus Patients and its Correlation With Microalbuminuria And Glycemic Control an a Tertiary Care Hospital in Eastern India

Dr Sujoy Barua[1]
[1]MBBS,MD. Specialist Medical Officer,Domkal Super speciality Hospital, Joyrampur, Domkal, Taraf Rasulpurpatnipara, West Bengal 742303
Corresponding Mail: Baruaandarka@gmail.com

Abstract

Background*: Type 2 diabetes mellitus (T2DM) is a longterm metabolic condition, which is characterized by high morbidity and mortality, mainly on account of its vascular complications. Plasma fibrinogen is an acute-phase reactant and a major coagulation factor shown to play a significant role in microvascular and macrovascular complications of diabetes.*

Objectives: *The objectives of the study were (i) to quantify fibrinogen plasma in patients with T2DM, and (ii) to determine the relation between fibrinogen and glycated control and microalbuminuria.*

Methods: *The cross-sectional observational study was carried out in the Department of General Medicine, Burdwan Medical College and Hospital, West Bengal, at 18 months (March 20203 August 2021). A total number of 160 patients with confirmed T2DM who were aged between 30 to 70 years were involved. There was hyper-detailed demographic, clinical, and biochemical data. The parameters of fasting and postprandial BG, HbA1c, lipid profile, plasma fibrinogen (Modified Clauss Method), and urinary albumin-to-creatinine ratio were measured. Data analysis was done through SPSS v24.0 by using independent t-test, ANOVA, and Pearson correlation; a p-value < 0.05 was taken as significant.*

Results: *The average value of plasma fibrinogen was 394.7+/-86.5 mg/dl and a significant percentage of the patients exhibited hyperfibrinogenemia. The mean level of fibrinogen was significantly higher in patients with poor glycemic control (HbA1c > 8%) as compared to those with HbA1c 39; ltgr jet Gill wholesome 8 percent (p < 0.05). Likewise, macroalbuminuric patients had considerably high fibrinogen than normoalbuminuric patients.*

Conclusion: *Fibrinogen levels in plasma are increased due to T2DM, and correlate significantly with low glycemic control and microalbuminuria. Fibrinogen can help in establishing patients at the highest risk of complications regarding a vascular-related problem, including the integration of it in the regular management of diabetics.*

Keywords: Plasma Fibrinogen; Glycemic Control; Microalbuminuria; Vascular Complications

1. INTRODUCTION

Diabetes mellitus (DM) is among the most common non-communicable long-term diseases and millions of people around the globe are living with it. It is a term that describes a set of metabolism disorders that are mainly characterized by sustained hyperglycemia caused by impairment of insulin secretion, insulin effect, or both. Diabetes has been termed a worldwide epidemic by the World Health Organization (WHO) and it has become very prevalent with an increasing trend especially in the low- and middle-income countries. Diabetes is estimated to impact more than 150 million persons in 2000, and this is predicted to triple by the year 2025 with each healthcare system bearing several economies and social costs due to diabetes [1].

India has become the hub of diabetes in the world and its prevalence has been increased because of urbanization, sedentary lifestyle, dieting habits and genetic risk factors. Development of gallstone disease (GSD) is one of the most under-recognized and common complications of uncontrolled diabetes. Gallstones are made up of both cholesterol, bilirubin and calcium salts and most often develop in the gallbladder; these can cause severe biliary problems including, cholecystitis, biliary colic and pancreatitis. Gallstones are especially prone to elderly women with type 2 diabetes mellitus (T2DM) because of the hormonal effects, stagnant gallbladder emptying, and dyslipidemia [2], [3].

The relationship that exists between diabetes and the development of gallstones is multifactorial. The main mechanisms between these conditions are insulin resistance, changed lipid metabolism, hypomotility of the gallbladder, and obesity. There is the prevalence of Gallstones in diabetic populations

compared to non-diabetic which has been reported at a greater number of epidemiological studies. Moreover, older women tend to have silent gallstones that can develop to reach the climax of the illnesses and exist without significant symptoms until the cases develop [4], [5].

The world health organization (WHO) estimates that by 2030 diabetes will be the seventh killer in the world. Increased incidence of both Type 2 diabetes mellitus (T2DM) and obesity has had a close-knit relationship with shifting lifestyles, less physical activity and the growing urbanization [1]. Both genetic and environmental factors contribute to the development of a prominent metabolic disorder, T2DM, and it is strongly associated with micronutrient imbalance, i.e., trace elements, including zinc and copper [6].

This zinc and copper homeostasis play a crucial role in a wide variety of biological processes, such as antioxidant protection, insulin production, and immune response. Trace minerals such as zinc have been found to play a role in the metabolism of insulin, and copper plays a role in enzyme redox reactions. Aberrations of their serum levels as well as the serum levels of diabetic individuals have been discussed, particularly in cases where these patients exhibit the condition of obesity as a complication of the condition [6]. It is widely known that oxidative stress contributes to pathogenesis of diabetes. During obesity, a low-grade, chronic inflammatory state that is associated with a net production of reactive oxygen species (ROS) contributes to elevated oxidative damage [7].

A review of literature has reported an inverse relationship between concentrations of serum zinc and copper and glycemic control. Because of the appearance of hyperzincuria, the levels of zinc will presumably decrease in patients with T2DM, and the levels of copper can rise, which can partially justify the increase in oxidative burden [8]. In turn, the imbalance of trace elements production may not merely become the outcome but one of the causes of the metabolic derangement observed in diabetes [9]. The study showed that diabetic patients possessed substantially low levels of serum zinc and comparatively high copper than the normal control groups did [10].

The reports provided by National Nutrition Monitoring Bureau (NNMB) and Indian Council of Medical Research (ICMR) have indicated that Indians populations are susceptible to poor diets and social and economic disparities as a factor that promotes the micronutrient deficiency particularly in India [11]. In this case, the nutrition transition of increased consumption of commercially processed foodstuffs and a concomitant reduction in the calorie-dense traditional foods is manifested in urban and semi-urban Indian populations who experience both obesity and micronutrient malnutrition at the same time posing a challenge to food security efforts in the country which, in real terms, translates directly to both obesity and micronutrient deficiency as Indians consume more processed foodstuffs and less of the nutrient-rich traditional Indian foods [12-13].

India has the second-highest population of diabetics, and between this segment, an increased prevalence of diabetic patients is classified as obese diabetics, especially in urban regions [14]. Central adiposity is an important deterioration factor of insulin resistance and metabolic outcome. The synergistic relationship between diabetes-related complications and obesity has been explored in biomarker studies, which examine parameters such as BMI, waist circumference, and even, trace elements such as zinc and copper [15].

In addition, the imbalance of trace elements is being developed as the predictive factor of the diabetes complications like nephropathy, neuropathy and cardiovascular diseases. Trace metal dysregulation may be involved in the pathophysiology of vascular endothelial damage, a primary cause of diabetic morbidity due to oxidative stress [16]. Hence, the profiling of these micronutrients may have an early prognostic value and assist in optimizing personalized nutritional supplements in diabetic patients, particularly those who have obesity [17].

The connection between the occurrence of diabetes mellitus and the trace elements i.e. zinc and copper, has attracted quite some interest amongst the scientific community over the past few years. Zinc is found to have significant roles in stability and activity of insulin. It plays a vital role in the manufacture, storage and secretion of insulin in the pancreas 8 beta cells. Numerous studies indicated that Zinc deficiency hinders glucose tolerance, and exacerbates oxidative stress thereby enhancing the occurrence and development of diabetes mellitus [18]. Copper on the other side is a constituent of many enzymatic pathways, such as cytochrome oxidase and superoxide dismutase and has been shown to undergo processes of redox. Increased copper has been clinically described in diabetic patients and their height has been proposed to aid the production of free radicals and oxidative stress, deteriorating diabetic complications [19].

It is not only the disturbance of the balance of these trace elements in the human body that influences glucose metabolism but also the pathophysiology of obesity-related type 2 diabetes. The metabolic disorders clash with oxidative stress and chronic inflammation tending to cause a lower level of serum zinc and higher level of serum copper in obese diabetic people compared to non-obese diabetic patients [20]. Therefore, research into the connections of these trace elements, obesity and glycoprotein control may enable to obtain the useful information on the prevention and treatment of diabetes and related complications.

Although there is an expanding literature, paucity of data relating to the interaction between zinc and copper levels and obesity in diabetic populations are found in eastern India. A good percentage of the available literature has been conducted in Western or Southern regions of the country which has a gap in the evidence level about the existence of the populations in West Bengal. The aforementioned regional disparity is the support that the current study needed, as it was conducted to assess the serum level zinc and copper in obese diabetic patients and measure the correlation between these parameters and glycemic parameters. By filling this knowledge gap, the proposed study would support the formulation of more elaborate management approach, with particular focus on micronutrient surveillance within the diabetic practice [21].

2. MATERIALS AND METHODS

2.1 Study Design and Setting

It was cross-sectional observational study at the Department of General Medicine, Burdwan Medical College and Hospital, West Bengal. Both the inpatients of the wards and outpatient diabetic clinic were recruited as patients. The work lasted 18 months (March 2020 to August 2021), and within this timeframe, they conducted preparations, data collecting, analysis and report writing.

2.2 Study Population and Sample Size

The sampled population included patients with type 2 diabetes mellitus. This was done through sample size calculated as n = 4pq/d 2, which is sufficient to provide adequate statistical power to identify clinically significant correlations.

2.3 Inclusion criteria:

- Patients with a confirmed diagnosis of T2DM, either newly diagnosed or already on treatment.
- Age between 30 and 70 years.
- Both male and female patients.

2.4 Exclusion criteria:

- Patients with type 1 diabetes mellitus.
- Pregnant or lactating women.
- Patients with nephrotic syndrome, chronic inflammatory disorders, or malignant conditions.
- Individuals with acute myocardial infarction (<4 weeks), congestive cardiac failure, or known hepatic disease.
- Patients with habits of smoking or alcoholism.
- Patients on medications influencing fibrinogen levels (e.g., warfarin, corticosteroids, or hormonal therapy).
- Patients not compliant with treatment or follow-up protocols.

This rigorous inclusion–exclusion framework minimized confounding variables and ensured the reliability of observed associations.

2.5 Parameters Studied

Detailed biochemical and clinical assessment was performed in all the participants. Categories of information gathered entailed socio-demographic information, presence of hypertension history, smoking/alcohol consumption, and anthropometry. The next studies were carried out:

1. Fasting Blood Sugar (FBS) and Postprandial Blood Sugar (PPBS).
2. Glycosylated Hemoglobin (HbA1c) – assessed using cation exchange resin method.
3. Complete Hemogram.
4. Serum Urea and Serum Creatinine.
5. Urine routine examination.
6. Fasting Lipid Profile.
7. Plasma Fibrinogen level (mg/dl) – estimated by the Modified Clauss Method.
8. Urinary Albumin-to-Creatinine Ratio (UACR) to detect microalbuminuria.

9. Electrocardiogram (12-lead with long lead II).

2.6 Study Tools and Instruments

Data collection was facilitated by:

- A semi-structured predesigned questionnaire to capture socio-demographic and clinical details.
- A study schedule for uniform data entry.
- Standardized instruments including measuring tape, calibrated weighing machine, and sphygmomanometer.
- Sterile sample collection kits for venous blood and urine samples.

2.7 **Statistical Analysis**

All collected data were initially tabulated in Microsoft Excel and subsequently analyzed using SPSS software version 24.0**.** Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as percentages.

The following statistical tests were applied:

- Independent t-test**:** for comparing mean values between two groups.
- One-way ANOVA**:** for comparing multiple group means.
- Pearson's correlation coefficient**:** for assessing the relationship between plasma fibrinogen, glycemic indices (FBS, PPBS, HbA1c), and microalbuminuria (UACR).

A p-value ≤ 0.05 was considered statistically significant.

2.8 Ethical Considerations

This study was assessed and granted by the Institutional Ethics Committee (IEC), Burdwan Medical College and Hospital. All the participants signed an informed consent form prior to the enrollment. During the study, patient information was handled as a strict matter of secrecy. All the activities were conducted in the light of the ethical principles expressed in the Declaration of Helsinki.

3. RESULT AND ANALYSIS

Table 1: Demographic Profile of Respondent

Variable	Category	Frequency (n)	Percentage (%)
Age (years)	40–50	44	27.5
	51–60	40	25
	61–70	76	47.5
Sex	Male	96	60
	Female	64	40
BMI (kg/m²)	Normal (<25)	64	40
	Overweight (25–29.9)	61	38.1
	Obese (≥30)	35	21.9
Hypertension	Present	59	36.9
	Absent	101	63.1
History of smoking	Yes	18	11.3
	No	142	88.7
Alcohol intake	Yes	19	11.9
	No	141	88.1

Demographic investigation in the sample population (n = 160) gives essential information on the nature of the patients diagnosed with type 2 diabetes mellitus. There was an evident preponderance of males (60 males against 40 females resulting in a ratio of 1.5:1 between males and females). The average age of the participants was 54.8 +/- 9.3 years and the greatest proportion was those in the 61-70-year range (47.5). This underscores the fact that diabetes is more common among the elderly as its natural course consists of the pathology as a long-lasting progressive disease of the metabolism.

The anthropometric measures showed that only 40% of the patients had normal BMI with majority finding themselves being overweight (38.1%) and obese (21.9%). The facts that almost 6 out of every 10 respondents had excess body weight is a clear indicator that diabetes and obesity are closely related. Additionally, central obesity was high especially on the group of female respondents thereby presenting

gender-specific risk patterns. Patients were also likely to have one of these conditions: comorbidities (36.9%) of the patients had comorbid hypertension, which added to their cardiovascular risk. Smoking, alcohol consumption, were lifestyle factors, and were exclusive to male patients (11.3, 11.9, respectively). In general, the demographic characteristic shows the prevalence of middle-aged to old participants in the study with high prevalence of obesity and hypertension which are well-known factors in exacerbating and propagating type 2 diabetes mellitus.

On the basis of objective of the Study

Objective 1: To study Plasma Fibrinogen levels in patients with type 2 Diabetes Mellius.

Table 3. Plasma fibrinogen levels among study participants

Parameter	**Mean ± SD (mg/dl)**	**Normal Range (mg/dl)**
Plasma Fibrinogen Level	394.7 ± 86.5	200–400

The mean fibrinogen concentration of the plasma of the type 2 diabetes patients used in the present study was 394.7 +- 86.5 mg/dl, which falls within the upper range of the physiological limit. The large part of patients presented with values >400 mg/dl characterized by hyperfibrinogenemia and underlining the pro-thrombotic condition associated with diabetes. This is in line with earlier findings that fibrinogen is an inflammatory marker as well as indicator of cardiovascular risk.

Study can attribute the underlying mechanism to chronic hyperglycemia that is associated with stimulation of oxidative stress, endothelial dysfunction, and systemic inflammation and hence increase hepatic production of fibrinogen. An abnormal level of fibrinogen raises blood viscosity level, platelet adhesion and clumping, and cause tendency to coronary artery diseases and stroke. Further, elevated fibrinogen can worsen microvascular complication including nephropathy and retinopathy. Therefore, fibrinogen becomes biomarker clinically significant in terms of assessing metabolic and vascular burden related to diabetes and should, thus, be monitored early to restrict late complications.

Objective 2: To study the correlation of Plasma Fibrinogen levels with Glycemic control and Microalbuminuria in patients with type2 Diabetes Mellitus.

Table 4. Glycemic parameters and plasma fibrinogen levels

Parameter	**Mean ± SD**	**Reference Range**
Fasting Blood Sugar (mg/dl)	156.2 ± 34.7	70–110
Postprandial Blood Sugar (mg/dl)	239.5 ± 42.6	<140
HbA1c (%)	8.4 ± 1.2	<6.5
Plasma Fibrinogen (mg/dl)	394.7 ± 86.5	200–400

A prevalence of 51.8 of microalbuminuria on the male respondents in the study once again confirmed the high incidence of microalbuminuria as an early indicator of diabetic nephropathy as well as endothelial dysfunction. The result showed that the level of plasma fibrinogen was significantly higher in microalbuminuria group (426.3 +/ - 68.7 mg/dl) than normoalbuminuric (348.6 +/ - 52.4 mg/dl), and was statistically significant. This signifies there is a remarkable correlation between high fibrinogen and the involvement of the kidney in type 2 diabetes.

Microalbuminuria is the indicator of glomerular damage and amplified vascular permeability, connected with the systematic inflammation. As fibrinogen increases, renal damage can be complemented, due to the increase in blood viscosity, the impairment of microcirculation, and the process of platelet aggregation in glomeruli. In contrast, microalbuminuria is by itself an indication of endothelial dysfunction, which can also abet the production of fibrinogen in the liver.

These results clinically bring to the fore fibrinogen as a dual biomarker of metabolic and renal stress. Fibrinogen measurement at T0 combined with urine albumin can enhance the early detection of high-risk patients and inform intervention to prevent diabetic complications

Table 5. Plasma fibrinogen levels in relation to microalbuminuria

UACR Category	**n** (%)	**Mean Plasma Fibrinogen (mg/dl) ± SD**
Normoalbuminuria (<30 mg/g)	77 (48.2%)	348.6 ± 52.4
Microalbuminuria (30–300 mg/g)	83 (51.8%)	426.3 ± 68.7

The study revealed that microalbuminuria, considered a sign of early diabetes nephropathy and endothelial dysfunction showed a percentage of 51.8 of the participants. Fibrinogen level was markedly elevated in this population (426.3 68.7 mg/dl) compared to those with normoalbuminuria (348.6 52.4 mg/dl) and the difference was strongly significant, which indicates a close association of fibrinogen elevation with diabetes-affected kidneys.
Microalbuminuria is the indication of glomerular damage and the elevated vascular permeability, the processes that are closely stated with the systemic inflammation. Fibrinogen increase can potentiate renal damage because of increased blood viscosity, decreased microvascular blood flow and platelets adhesion in glomerular capillaries. Microalbuminuria, on the other hand is not only evidence of vascular abnormality, but may also contribute to increased fibrinogen production in a self-perpetuating loop of pathology.

Clinically, this underscores the importance of fibrinogen as a biomarker with two functionalities, metabolic and renal stress in the context of type 2 diabetes. The addition of fibrinogen test in addition to urine albumin analysis can facilitate the early detection of patients with high risks and enable preventive approach towards diabetic complications.

4. DISCUSSION

The given research proved that the level of plasma fibrinogen was significantly higher in type 2 diabetes mellitus patients and the average data show near the upper limits of the normal reference range. The significant fraction of patients had hyperfibrinogenemia (>400 mg/dl), which confirms the idea of diabetes-pro-thrombotic and inflammatory state. The same results have been already reported in the previous literature. King et al. have pointed out the world-wide burden of diabetes and underlined its co-relationship with vascular complications, which is facilitated by the distorted hemostatic factors, including fibrinogen [22].
It has been extensively explored on the correlation existing between fibrinogen and cardiovascular risk factors. The association with key coronary risk factors was found positive with plasma fibrinogen as reported by Lee et al. in the Scottish Heart Health Study which corresponds to the high fibrinogen concentrations found in our diabetic group population [23]. Moreover, Ceriello highlighted that chronic hyperglycemia has coagulation activation and increased fibrinogen concentration as contributing factors, which could explain the robust relationship between the fibrinogen level and poor glycemic control in the current study [24].
Study also noted renal involvement in our findings since patients with microalbuminuria showed much elevated levels of fibrinogen as compared to normoalbuminuric patients. This is in line with Dalla Vestra et al., who demonstrated that inflammatory markers such as fibrinogen are associated with glomerular structural modifications associated with diabetic nephropathy [25]. Accordingly, Gomes MB also found

correlations among acute-phase proteins and glucose status and fibrinogen [26], and Festa et al. have shown that subclinical inflammation increases insulin resistance and vascular dysfunction [27].
In short, Study demonstrated that plasma fibrinogen is a significant indicator of type 2 diabetes, strongly related to poor glycemic control and microalbuminuria and, in line with prior research.

5. CONCLUSION

In this study carried out at Burdwan Medical College and Hospital, the clinical importance of plasma fibrinogen as a biological marker in patients of diabetes mellitus-type 2 has been outlined. The results displayed that the average concentration of fibrinogen was significantly high and a substantial percentage of the patients showed hyperfibrinogenemia. This highlights the pro-thrombotic and inflammatory status that defines diabetes which lends credence to its involvement in the pathogenesis of vascular complications.
Notably, plasma fibrinogen was strongly related to poor glycemic control, which was estimated by HbA1c levels as well as the presence of microalbuminuria, the incipient stage of diabetic nephropathy. Fibrinogen was elevated in patients with microalbuminuria compared with those with normoalbuminuria and thus fibrinogen could be used as a dual biomarker of both metabolic dysregulation and renal involvement.
These data are concordant with prior studies and strengthen the data that fibrinogen is not only an acute-phase reactant but also has the potential to predict microvascular and macrovascular diabetic complications. Routine screening of fibrinogen and monitoring at the earliest stage and some of the established parameters of HbA1c and urinary albumin can be utilized to some extent to detect high-risk patients and implement timely interventions to prevent prolonged complications.
To sum up, plasma fibrinogen has important prognostic value in multifactorial management of type 2 diabetes and could be considered as additional instrument in standard treatment of diabetes.

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