

## Study of Fibrinogen Level in Type 2 Diabetes and Its Influence on Peripheral Arterial Disease

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**Abstract:** A study on the level of fibrinogen in Type 2 Diabetes patients and its influence on Peripheral Arterial Disease. Three groups (Group A- Diabetes patients, Group B- patients with DM+PAD, control group of healthy volunteers) of patients were included. Plasma fibrinogen level of all the patients were measured and is correlated with age, sex, BMI, WHR, HbA1C, FBS and ABI of the patients. PAD patients were identified with the help of ABI measurement. PAD is an expression of systematic atherosclerotic disease, if it is not diagnosed in the early stage it will lead to serious complications like Myocardial infarction, stroke and death. Role of haemostatic factors particularly Fibrinogen in vascular disorders has gained considerable interest. Comparatively increased fibrinogen concentration was seen in patients with both DM and PAD (414.97±28.73). We have also found that fibrinogen is increased in some diabetic patients with poor glycaemic control. This elevated fibrinogen can be considered as an indicator for cardiovascular disorders in diabetic patients. These results underline the possible relation between fibrinogen and presence of PAD in diabetic patients and thus the study reflects the importance of proper maintenance of glycaemic status in Diabetic patients.

**Keywords:** Body mass index, waist hip ratio, ankle brachial index, Fasting Blood sugar.

### INTRODUCTION

Diabetes is variable disorder of carbohydrate metabolism that may be caused by both hereditary and environmental factors. The disease is characterized by inadequate secretion or utilization of insulin [1].

It will produce glucose intolerance which will lead to hyperglycemia and alteration in the lipid, protein metabolism [2]. Compared with the general public, the mortality rate for people with diabetes is about twice that for people without diabetes [3].

The risk of developing atherosclerosis is higher in diabetic patients which are the most common cause for developing Peripheral Arterial Disease (PAD). PAD is a condition that is similar to coronary artery disease or carotid artery disease [4, 5]. The true prevalence of PAD in diabetic patients is difficult to determine because most of the patients remain asymptomatic. A number of patients do not report their symptoms, the screening modalities are also not uniformly agreed upon and the pain perception may be confused with peripheral neuropathy. One accurate method for determination of PAD is ABI measurement. PAD is five times more common in patients with diabetes than in patients without diabetes. Each 1% increase in glycosylated hemoglobin is associated with

a 28% risk of incident PAD [6]. So the early determination of PAD has greater clinical importance as it may increase the risk of MI, Stroke and death.

Fibrinogen is a coagulation protein which is an important determinant of blood viscosity and platelet aggregation [7]. There are a number of mechanisms that explains the increased concentration of plasma fibrinogen in diabetic patients. Since the glycosylated fibrinogen is less susceptible to plasmin degradation its level remains increased in diabetic patients with poor glycaemic control [8]. This increased plasma fibrinogen level leads to a state of hypercoagulability which contribute to the development and progression of atherosclerosis and it will increases the stroke risk associated with large aortic plaque [9]. Fibrinogen may be indirectly associated with vascular disease as a marker of unstable lesions that are undergoing subintimal hemorrhage or potent risk factors such as smoking [10].

Fibrinogen is also a cofactor in platelet activation and may directly contribute to plaque formation [4]. Hospital and epidemiological studies have reported elevated levels of plasma fibrinogen in patients with intermittent claudications [11]. Fibrinogen levels have been positively related to the degree of asymptomatic PAD. In PAD patients the monocytes infiltrating to the plaque get differentiated into macrophages that releases cytokines which increases the level of plasma fibrinogen. In such cases raised fibrinogen is predictive of future cardiovascular events particularly coronary death [12].

**METHODOLOGY**

It was a cross sectional comparative study, which was conducted in outpatient department of PKDAS Institute of Medical sciences, Vaniyankulam, Kerala, between august 2016 to September 2017. The study was approved by institutional ethics committee and informed consent was obtained from each patient after explaining the aims and procedures of the study. Data for the study was collected from the patient through interview and by reviewing the medical records. Patients who are already on drug therapy for Diabetes Patients who are having DM as well as Cardiovascular problems were included in the study. Whereas patients with any infection, advanced stages of PAD with pathological ABI values, Type 1 Diabetes patients, Type 2 Diabetes patients with smoking and alcohol habit were excluded. The data's are collected using specially designed data collection form physicians prescription records and laboratory results. Blood samples of the patients were collected in the fasting state for the determination of FBS, HbA1C and fibrinogen. PAD of the patients were determined with the help of ABI. It was measured with Vascular

Doppler recorder for ABI/TBI item code: Versalab LE. The primary objective of the study was to find out whether the fibrinogen level in DM patients influence the development of PAD, and the secondary objective was, what all the patient related factors that cause changes in the fibrinogen level and thus whether fibrinogen can be used as a predictive factor for the development of Diabetes related cardiovascular complications. All the data's were analyzed with Graph Pad software. All the continuous variables were presented as Mean ± SD. The comparison between two variables was done with the help of students T test. A P value of less than 0.05 is considered to be statistically significant. Pearson correlation coefficient value was determined using Microsoft Office Excel 2007. Independent predictors of fibrinogen level were analyzed using Multiple regression analysis.

**LIMITATION OF STUDY**

The small sample size of the study is a limitation, and so this study is primary in nature.

**RESULTS**

The study population included 60 Diabetic patients and 20 healthy volunteers (control group). Ankle brachial index measurement was performed in each subject; Presence of PAD was confirmed on the basis of ABI value. Thus the patients were divided into three groups (Group A- Diabetes patients, Group B- patients with DM+PAD, control group of healthy volunteers). The clinical characteristics of the patients are delineated in Table-1.

The mean fibrinogen level in different study groups are presented in Table-2, and it was found to be significantly higher in Group B than Group A and C.

**Table-1: Study Group Patients Characteristics**

Characteristics	Patients with DM	DM+PAD	CONTROL
NO. of cases	30	30	20
Mean age (year)±SD	57.6 ± 9.36	62.7±6.39	58.3±5.57
Male sex (n)	14	17	10
Female sex (n)	16	13	10
Waist hip ratio	0.97±0.089	1.04±0.091	0.95±0.087
Duration of DM(Mean±SD)	9.5±5.2	13.9±5.43	
Hypertension			
Yes	20	19	
no	10	11	
BMI(Mean±SD)	23.28±2.84	24.46±2.50	
FBS(Mean±SD)	147.38±42.90	185.64±62.28	
HbA1C(Mean±SD)	7.3±1.91	9.2±2.09	

**Table-2: Fibrinogen in Different Study Groups**

Group	Mean fibrinogen(mg/dl)±SD	n
Control (C)	256.9±54.59	20
DM (A)	341.79±73.35	30
DM+PAD (B)	414.97±28.73	30

Table-3 presents the correlation of fibrinogen with different variables in both Group A and Group B, these results show a significant positive correlation between BMI and Fibrinogen in both groups. Most

importantly the table shows a strong negative correlation between ABI value and plasma fibrinogen level.

**Table-3: Correlation of Fibrinogen with Different Parameter in Group A And Group B**

PARAMETERS	Coefficient of correlation r in GROUPA	Coefficient of correlation r in GROUPB
Age	0.0059	0.1863
BMI	0.2238	0.305
ABI	-0.458	-0.688
FBS	0.389	0.539
HbA1C	0.454	0.522
Waist hip ratio	0.047	0.0059

Table-4 shows correlation of fibrinogen with different parameters as a whole within the study population. On looking for association between

glycaemic control and fibrinogen level, it shows a strong positive correlation between both.

**Table-4: Correlation of Fibrinogen with Different Parameters In The Two Groups As A Whole**

Parameters	r value
Age (yrs)	0.191
BMI	0.287
ABI	-0.551
FBS (mg/dl)	0.467
HbA1C	0.534

In this study we have also determined the independent determinants of plasma fibrinogen with the help of multiple regression analysis. Here we have considered multiple variables such as age, BMI, Glycaemic control and ABI. Out of these 4 variables

examined ABI accounts for about 30% variation in the plasma fibrinogen level. Both FBS and HbA1C can also be considered as an independent determinant of Fibrinogen level as it is responsible for approximately 23% variation in fibrinogen concentration.

**Table-5: Stepwise Correlation of Fibrinogen with Various Determinants in Multiple Regression Analysis**

Parameter	R <sup>2</sup>
Age	0.006312
BMI	0.05543
FBS	0.2283
HbA1c	0.229
ABI	0.3190

Table-6 indicates the correlation between different variables within a group. Thus it shows a

strong negative correlation of ABI value with BMI, FBS and HbA1C.

**Table-6: Correlation between different parameters within Group A and Group B**

Parameters	Correlation (Group A)	P value (Group A)	Correlation (Group B)	P value (Group B)
BMI with PAD	-0.2764	<0.0001	-0.2123	<0.0001
BMI with HbA1C	0.124	<0.0001	0.0860	<0.0001
ABI with HbA1C	-0.358	<0.0001	-0.3704	<0.0001
ABI with FBS	-0.302	<0.0001	-0.3467	<0.0001

**DISCUSSION**

The increased prevalence of Type2 diabetes and related cardiovascular morbidity and mortality underscores the need to identify potential reversible cardiovascular risk factors in diabetic patients. In recent years, some haemostatic factors mainly fibrinogen has

gained much more attention as it has been implicated as a major reason for the development and progression of PAD [6, 7]. In our study we are trying to associate these two factors together with other Patient related parameters such as age, BMI, WHR, FBS, HbA1C. The increase in Plasma Fibrinogen level in diabetic patients

may be influenced by a number of factors. Here we are trying to correlate some of these patient related factors with fibrinogen since it acts as a strong independent risk factor for the development and progression of PAD. Both correlation and regression analysis were performed between the age, BMI, WHR, FBS, ABI and HbA1C of the patient with the fibrinogen level. On the basis of our observations the age of the patient cannot be considered as an important factor that influences the plasma levels of fibrinogen (Table-4). It may be due to the small sample size of the study population included in this study. The average BMI of the study population was  $23.86 \pm 2.72$ . Almost 30% of the study population shows over weight that is BMI > 24.9. Increase in BMI is associated with increased risk of metabolic disorders. However not all the patients with metabolic disorder is over weight or obese. In our study we have correlated BMI with Fibrinogen. The BMI is positively correlated with fibrinogen in both group A ( $r=0.223$ ) and B ( $r=0.305$ ) (Table-5). Study by Dr.Kafle, Sobia Ali, ArchanasachinBembde, etc., also shows similar observations [13, 14].

Waist hip ratio of individual patients was calculated on the basis of waist and hip measurements. In our study 20male patients and 25female patients show abnormal waist hip ratio, these values though they are significantly different among the groups, are not correlated with the plasma fibrinogen level in Diabetic patients ( $r=0.047$ ) as well as in patients with DM+PAD ( $r=0.059$ ) (Table-3).

Diabetic patients are at a greater risk to develop Peripheral arterial disease due to the hyper-reactivity of platelets, increased activation of prothrombotic coagulation factors and decreased fibrinolysis [4]. In this study it clearly shows an increase in mean fibrinogen level in diabetic patients ( $341.79\text{mg/dl} \pm 73.35$ ) and in patients with diabetes and PAD ( $414.97\text{mg/dl} \pm 28.73$ ) as compared to the control group subjects ( $256.9 \pm 54.59$ ) (Table-2). Out of 30 diabetic patients 5 of them show an increased fibrinogen level than the normal. It may be due to the poor glycemic control, older age of the patients, long duration of diabetes or may be due to some underlying factors that influence plasma fibrinogen level. Study by Dr. Kafle and J. V. Mahendra shows increased fibrinogen levels in patients with diabetes and PAD and some patients with diabetes only [12, 14]. Furthermore a study by Marijan Bosevski shows fibrinogen increases atherogenic dyslipidaemia in diabetic patients. Increased fibrinogen is seen in diabetic patients on oral hypoglycemic agents as well as on insulin therapy<sup>7</sup>. Fibrinogen as compared with other inflammatory biomarkers more closely associated with diabetic vascular diseases [7]. HbA1C values have been reported to be an important independent predictor plasma fibrinogen concentration in Type 2 DM patients. The study by Ceriello A gives evidence that fibrinogen

concentrations can be reduced by proper glycaemic control of patients [15]. In our results also fibrinogen shows a strong positive correlation with the HbA1C values. In a total of 60 diabetic patients 39 of them show abnormal HbA1C values. As the value of HbA1C increases fibrinogen level also increases (Table-3) in both group A ( $r=0.454$ ) and group B ( $r=0.522$ ) (Table-5). When we consider both groups as a whole it also showed a strong positive correlation ( $r=0.534$ ) between fibrinogen and HbA1C values (Table-4). A number of clinical studies also showed similar observations. There are various possible mechanisms that accounts for hyperfibrinogenemia in patients with poor glycaemic control. PAD is a major risk factor for lower extremity amputation especially in patients with diabetes. Even for asymptomatic patients PAD is a marker for systemic vascular disease involving coronary, cerebral and renal vessels leading to an elevated risk events such as myocardial infarction, stroke and death. In this study we are trying to associate the influence of Fibrinogen in the development of PAD. Our observations show an increase in fibrinogen level in PAD patients. Here it show an increase in fibrinogen level in patients who are having lower ABI values ie., the patients with peripheral arterial disease. Diabetes increases the risk of atherogenesis by deleterious effect on the vessel wall and also by producing abnormalities in the rheology [4]. ABI shows a significant negative correlation with the fibrinogen level. It is relevant in both Group A ( $r=0.458$ ) and Group B ( $r=0.688$ ) (Table-3). While considering two groups as a whole also it shows a perfect negative correlation ( $r=-0.551$ ) (Table-4). So that the maintenance of plasma fibrinogen level by the proper control of various reversible factors like glycaemic status of the patients, BMI, etc., are very important. Here we performed multiple regression analysis to identify independent significant independent determinants of fibrinogen. According to our observations age ( $r^2=0.0063$ ), and BMI ( $r^2=0.0554$ ), do not change the power of predicting plasma Fibrinogen level, Where as FBS ( $r^2=0.228$ ) and HbA1C ( $r^2=0.229$ ), can act as a strong determinant for abnormal plasma fibrinogen level. Whereas ABI accounts for 32% variability in fibrinogen level ( $r^2=31.90$ ) (Table-5).

## CONCLUSION

The results obtained from our study indicate that plasma fibrinogen level in diabetic patients with or without PAD are relatively higher than the control group. Plasma fibrinogen level can independently influence the progression of PAD and so the determination of plasma fibrinogen may be used as a marker in predicting the development of peripheral arterial disease and related complications. HbA1C and plasma fibrinogen levels are positively correlated to each other and so proper glycaemic control of the patient is essential for preventing the serious macro and micro vascular complications associated with T2DM.

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