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Plasma Fibrinogen As A Marker Of Vascular Ischemia In Type 2 Diabetes Mellitus.

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ABSTRACT

Fibrinogen is known as "primarily thrombosis marker" as it promotes fibrin formation and contributes to plasma viscosity and it is directly proportional to plasma protein concentration Fibrinogen an acute phase reactant helps in clot formation in response to vascular injury. The present study demonstrates increased Fibrinogen level in diabetic group. This might be one of the risk factor for the onset of initiation of cardiovascular risk and also emphasizes the importance of assessing this marker for the early diagnosis and therapeutic interventions. So it is reasonable to include Fibrinogen in the Cardiovascular risk profile of diabetic patients. To determine plasma Fibrinogen levels, hs CRP levels, HbA1c levels and biochemical parameters among 30 IHD, 30 DM and 30 healthy controls attending OPD at our Medical College and Hospital. Informed consent was taken prior to conduct of sample collection and samples were analysed. The mean value of plasma Fibrinogen in DM with IHD (289.323±44.7744), group DM(338.047±65.0022) and healthy controls (365.487±59.7479) were significant (p=<0.001). The study also suggests that fluctuations in glycaemia, as evidenced by increased HbA1c in DM, can also have an impact on the plasma Fibrinogen levels.

Keywords: Diabetes Mellitus, Ischemic Heart Disease, Plasma Fibrinogen, HbA1c,hs CRP

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INTRODUCTION

World Health Organization (WHO) has reported that about 422 people have Diabetes (DM) worldwide, who exist in low and middle income countries and 1.5 million deaths are directly related to DM each year (1). As per WHO, 77 million people above 18 years of age are of type 2 DM in India. There are 25 million people with pre diabetics and 50% of people are unaware of DM status which is a health threat. Adults with DM are more prone to micro and macrovascular incidences (2). Fibrinogen is been reported as a cause of atherosclerosis in DM patients especially type 2 DM (3). Thrombogenesis and inflammation are both characterized by the biomarker Fibrinogen, which is mostly produced by hepatocytes (4,5). Fibrinogen is known as "primarily thrombosis marker" as it promotes fibrin formation and contributes to plasma viscosity and it is directly proportional to plasma protein concentration. In addition, Fibrinogen participates in the regulation of blood viscosity. Hyper viscosity has been shown to be an important component of microcirculatory disorder in Diabetes. Finally, Fibrinogen is an acute phase reactant that is increased in inflammatory status.

At the diagnosing stage of DM, there is more evidence of micro and macro vascular disease in Asians when compared to Europeans(6,7). DM is also an independent influencer of atherosclerosis which is responsible for more than 50% of death in type 2DM patients(8). Hyperglycemia which is persistent in DM leads to both micro and macro vascular chaos inclusive of organ damage and eventually Coronary Artery Disease (CAD). There is a strong association of DM and cardio vascular disease(CVD) that has led to hypothesis that both originate from common factors like insulin resistance, obesity, dyslipidemia and hypertension(9,10). The serum hsCRP (high sensitive C reactive protein) is another known inflammatory marker which is increased in DM patients. Ritu Gupta et al reported the hsCRP levels were higher in DM patients and correlated with duration of DM and HbA1c which was associated with macro vascular complications(11).

The aim of our study was conducted to determine the level of plasma Fibrinogen in our study groups and to correlate it with hsCRP, HbA1c and biochemical parameters.

MATERIALS AND METHODS

Study design

The study was carried out during the period may 2018-Nov 2019. It was done in 3 groups, namely, apparently healthy controls as group 1, diabetic individuals (DM) as group 2 and diabetic subjects with Ischemic Heart Disease (IHD) as group 3. Based on the inclusion and exclusion criteria the participants were selected. Institutional ethical committee clearance was obtained.

Participant selection criteria

Patients with confirmed diagnosis of IHD with DM based on history and previous blood investigations reports were included in the study. Exclusion criteria were pregnant women, malignancy, acute infections, smoking or alcoholic and liver disease. All the patients were recruited from our Medical College, Chennai (Figure 1).

Sample collection

7 ml of peripheral venous was withdrawn from all the study subjects under sterile conditions with disposable blood syringes after overnight fasting. Two ml of blood was transferred into the test tube containing EDTA for HbA1c estimation, two ml of blood was transferred into the test tube containing sodium citrate for plasma Fibrinogen estimation, one ml of blood was transferred to a pinch of potassium oxalate and sodium fluoride (3:1 mixture) for plasma glucose estimation. The remaining 2 ml of blood was transferred to a plain tube.

Serum separated from this tube was pipetted into a centrifuge tube and was centrifuged at 2500 revolutions per minute for 5 minutes, to get clear serum without any cells.1 ml of the above serum was stored at –20 C for the estimation of serum hsCRP. From the remaining serum, parameters such as Urea, Creatinine, serum triglycerides, total cholesterol, HDL and liver function tests were measured within 6 hours of blood collection by enzymatic methods using commercial kits. Height (in cms) and Weight (in kgs)

of the subjects were measured to calculate the body mass index. Waist and hip circumference were measured to calculate waist/ hip ratio. The biochemical parameters undertaken for the study were determined using the auto analyzer (Transasia xl 640).

RESULTS

Table 1 represents the mean age, waist circumference, BMI, diastolic BP among all three groups were not statistically significant. The mean value of systolic blood pressure in group 1 (104.00+9.32), group 2(112.00+13.49) and group 3 (111.33+13.58) were significant (p-value 0.024). All the groups are age & BMI matched.

The group 1 consists of 30 subjects (33.3%) with 12 male (31.6%) and 18 female (34.6%). The group 2 consists of 30 subjects (33.3%) with 13 male (34.2%) and 17 female (32.7%). The group 3 consists of 30 subjects (33%) with 13 male (32%) and 17 female (32.7%). All the groups are age and gender matched.

Table 2 represents the biochemical parameters among the three groups. The mean value of blood glucose in group 1 (86.667±10.1755), group 2(176.931±82.1721) and group 3 (141.016±59.6510) were significant (p-value<0.001). The multiple comparison of FBS by **Tukey HSD Post Hoc Tests for Multiple Comparisons** between the three groups, shows that the mean difference of FBS (54.349) between the group 3 and group 1 was significant (p-value 0.002).The mean difference of FBS (90.265) between group 1 and group 2 was significant (p-value 0.000) . The mean value of blood urea in group 1 (20.97±4.30), group 2 (21.51±4.71) and group 3 (26.24±7.77) were significant (p-value 0.001). The multiple comparison of urea level by **Tukey HSD Post Hoc Tests for Multiple Comparisons** between the groups shows that the mean difference of urea (4.737) between group 3 and group 2 was significant (p-value 0.006) and the mean difference of urea level (5.276) between group 3 and group 1 was significant (p-value 0.002). The mean creatinine level among all the three groups were not statistically significant. The mean albumin values among all the groups were not statistically significant. The mean uric acid in group 1(4.48±1.24, group 2 (7.50±0.73) and group 3 (6.70±1.50) were significant (p=<0.001). The multiple comparison of uric acid by **Tukey HSD Post Hoc Tests for Multiple Comparisons** between the groups shows that the mean difference of uric acid (2.213) between group 3 and group 1 was significant (p=<0.001) and the mean difference of uric acid (3.013) between group 2 and group 1 was significant p=<0.001). The mean calcium among all the three groups were not statistically significant.

The mean level of cholesterol was group 1 (176.80±26.084), group 2(170.50±37.546) group 3 (176.23±37.043) were not statistically significant. The mean TGL level in group 1(129.283±23.9005), group 2 (251.900±86.3251) and group 3 (192.867± 88.4716). The mean of TGL among all the three groups were significant (p-value <0.001). The multiple comparison of TGL by TUKEY HSD Post HOC Test between the three groups shows the mean difference of TGL (-59.033) between group 3 and group 2 (p =0.006), group 3 and group 1 were significant (p=0.003). The mean difference of TGL (122.617) between the group 2 and group 1 was significant (p=<0.001). The mean HDL in group 1(35.81±4.89), group 2(34.61±6.64) and group 3(31.33±6.22) were significant (p=0.013). The multiple comparison of HDL by **Tukey HSD Post Hoc Tests for Multiple Comparisons** between the groups shows that the mean difference of HDL (-4.479) between group 3 and group 1 was significant (p=0.013). The mean LDL in group 1(114.29±25.97), group 2(83.28±30.01) and group 3 (104.99±36.72) were significant (p=0.001). The multiple comparison by **Tukey HSD Post Hoc Tests for Multiple Comparisons** between the three groups shows that the mean difference of LDL (21.712) between group 3 and group 2 was significant (p=0.023) and the mean difference of LDL (-31.010) between group 2 and group 1 was significant (p=0.001). The mean VLDL in group 1(25.857±4.78), group 2(50.360±17.29) and group 3(38.553±17.68) were significant (p=<0.001). The comparison of VLDL by **Tukey HSD Post Hoc Tests for Multiple Comparisons** between the groups shows that the mean difference of VLDL (-11.807) between group 3 and group 2 was significant (p=0.006) and the mean difference of VLDL (12.697) between group 3 and group 1 was also significant (p=0.003).

Table 3 represent mean hsCRP and HbA1c among all the three groups. The mean hsCRP in group 1 (1.75 ±0.79), group 2(6.07±2.24) and group 3 (4.38±2.26) were significant (p=<0.001).The multiple comparison of hsCRP by **Tukey HSD Post Hoc Tests for Multiple Comparisons** between the three groups. The mean difference of hsCRP (-1.688) between group 3 and group 2 was significant (p=0.002), the mean difference of hsCRP (2.635) between group 3 and group 1 was significant (p=<0.001) and the mean difference of hsCRP between group 2 and group 3 was significant (p=<0.001). The mean HbA1c among all

the three groups. The mean HbA1c in group 1 (5.79±0.64), group 2(9.72±2.05) and group 3(8.92±1.47) were significant (p=<0.001). The mean difference by **Tukey HSD Post Hoc Tests for Multiple Comparisons** of HbA1c (3.129) between group 3 and group 1 was significant (p=<0.001) and the mean difference of HbA1c (3.924) between group 2 and group 1 was significant (p=<0.001).

The table 4a consists, comparison of plasma Fibrinogen among the study group and controls. The table 4b represent plasma Fibrinogen levels in all the three groups. The mean value of plasma Fibrinogen in group1 (289.323±44.7744), group 2(338.047±65.0022) and group 3 (365.487±59.7479) were significant (p=<0.001). Table 4(b) **Tukey HSD Post Hoc Tests for Multiple Comparisons**. The multiple comparison of plasma Fibrinogen among (DM) controls and study group. The mean difference by **Tukey HSD Post Hoc Tests for Multiple Comparisons**. The mean difference of HbA1c (76.1633) between group 3 and group 1 was significant (p=<0.001). The mean difference of HbA1c (48.7233) between group 2 and group 1 was significant (p=0.004).

The Table 5 shows the correlation between plasma Fibrinogen and HbA1c and plasma Fibrinogen versus hsCRP. This shows that plasma Fibrinogen level is strongly correlated with HbA1c and hsCRP with a significant p-value(0.002 and 0.003). The ROC curve (figure 2), shows the cut off value of plasma Fibrinogen level that predicts the risk for CAD. Area under the curve is 0.776 and the cut-off value is 315.6. Plasma Fibrinogen ≥ 315.6 favours IHD in DM patients. The parameter plasma Fibrinogen shows sensitivity of 70.00%, specificity of 83.33%, positive predictive value of 89.36%, negative predictive value of 58.14 and has diagnostic accuracy of 74.44%.

Figure 1 represent the groups included in the study

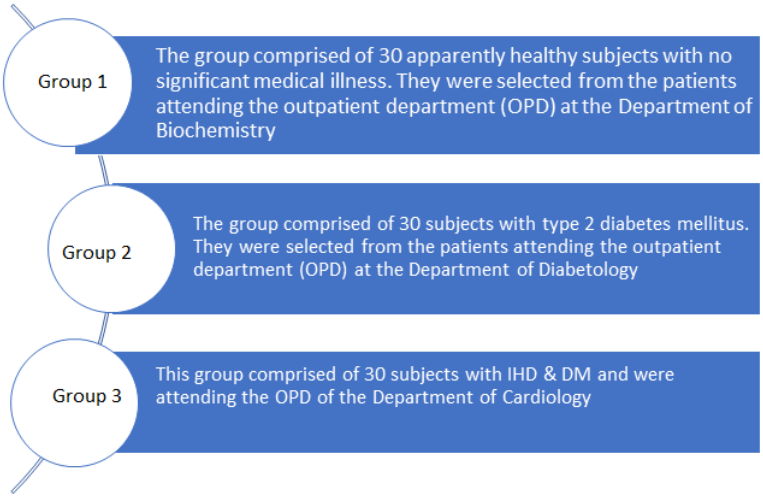
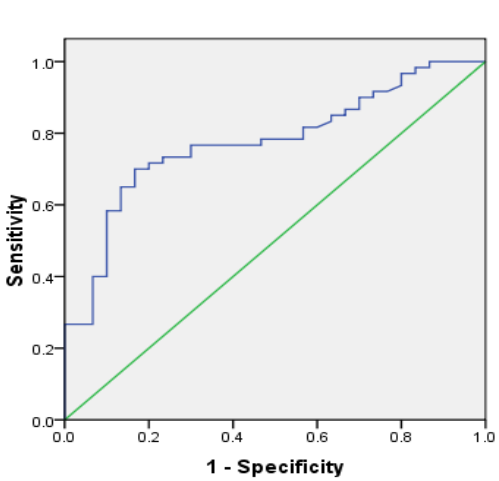


Figure 2 represent ROC Curve to find the cut-off value of Pl. fibrinogen to classify DM+IHD



Area under the Curve is 0.776 and the cut-off value is 315.6 (if Pl. fibrinogen ≥ 315.6 favors for DM + IHD)

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Table 1 represents the demographic features among the groups

	Groups	Mean	S D	p-value
Age	Group 1	55.30	7.120	0.841
	Group 2	55.20	6.880	
	Group 3	54.33	9.979	
BMI	Group 1	23.75	2.73	0.150
	Group 2	25.50	5.64	
	Group 3	25.61	3.39	
Waist circumference	Group 1	97.40	4.52	0.149
	Group 2	100.27	11.07	
	Group 3	96.18	8.02	
Systolic BP	Group 1	104.00	9.32	0.024
	Group 2	112.00	13.49	
	Group 3	111.33	13.58	
Diastolic BP	Group 1	79.00	9.60	0.726
	Group 2	79.33	10.81	
	Group 3	81.00	10.62	

Table 2 represent mean level of biochemical parameters among the three groups.

	Groups	Mean	Standard Deviation	p-value
Glucose	Group 1	86.667	10.1755	<0.001
	Group 2	176.931	82.1721	
	Group 3	141.06	59.6510	
Urea	Group 1	20.97	4.30	0.001
	Group 2	21.51	4.71	
	Group 3	26.24	7.77	
Creatinine	Group 1	1.013	1.325	0.641
	Group 2	0.823	0.128	
	Group 3	0.947	0.314	
Albumin	Group 1	4.310	.3458	0.357
	Group 2	4.463	.5236	
	Group 3	4.417	.3742	
Uric acid	Group 1	4.48	1.24	<0.001
	Group 2	7.50	0.73	
	Group 3	6.70	1.50	
Calcium	Group 1	10.21	0.245	0.992
	Group 2	10.20	0.166	
	Group 3	10.21	0.245	
HDL	Group 1	35.81	4.89	0.013
	Group 2	34.61	6.64	
	Group 3	31.33	6.22	
LDL	Group 1	114.29	25.97	0.001
	Group 2	83.28	30.01	
	Group 3	104.99	36.72	
VLDL	Group 1	25.857	4.78	<0.001
	Group 2	50.360	17.29	
	Group 3	38.553	17.68	
TGL	Group 1	129.283	23.9005	<0.001

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	Group 2	251.283	86.3251	
	Group 3	192.867	88.4716	
Total Cholesterol	Group 1	176.80	26.084	0.730
	Group 2	170.50	37.546	
	Group 3	176.23	37.043	

Table 3 represent the mean values of HS CRP and HbA1c between groups.

	Group	N	Mean	Std. Dev	Minimum	Maximum	P-Value
HS CRP	DM + IHD	30	4.38	2.26	1.026	9.134	<0.001
	DM	30	6.07	2.24	1.515	9.624	
	Control	30	1.75	0.79	0.262	3.174	
	Total	90	4.06	2.59	0.262	9.624	
HbA1c (%)	DM + IHD	30	8.92	1.47	6.9	14.0	<0.001
	DM	30	9.72	2.05	5.6	14.4	
	Control	30	5.79	0.64	4.6	6.9	
	Total	90	8.14	2.26	4.6	14.4	

Table 4a represents One way ANOVA to compare mean Pl. fibrinogen level between groups

Group	**N**	**Mean**	**Std. Dev**	**Min**	**Max**	**P-Value**
DM + IHD	30	365.487	59.7479	238.5	493.2	<0.001
DM	30	338.047	65.0022	247.9	497.9	
Control	30	289.323	44.7744	210.4	393.4	
Total	90	330.952	64.7791	210.4	497.9	

Table 4 b represents the mean difference of plasma fibrinogen between the three groups

Group	Group	Mean Difference	Sig.
DM + IHD	DM	27.4400	0.157
	Control	76.1633	<0.001
DM	Control	48.7233	0.004

Table 5 represents the Correlations between plasma fibrinogen, HbA1C and Hs CRP

Correlation between	Correlation	P-Value
Plasma fibrinogen vs HbA1c (%)	0.324	0.002
Plasma fibrinogen vs HS CRP	0.307	0.003

DISCUSSION

In this study, we attempted to explore the role of plasma Fibrinogen in the development of ischemic heart disease in type 2DM. The Diabetics and controls were matched with respect to the confounding variables like age gender and BMI. The biochemical parameters and physical parameters were done for all the three groups. Among the parameters, fasting blood glucose, urea, HDL, TGL, VLDL, LDL, uric acid, hsCRP, systolic blood pressure, plasma Fibrinogen, HbA1c were statistically significant between the groups.

The plasma Fibrinogen levels was increased in group 2 and was found to be statistically significant (p= <0.001). Several prospective, epidemiological studies from Goteborg, Sweden, London and Framingham study have identified elevated Fibrinogen as a risk for Cardio Vascular Disease. In the Northwick Park Heart study, haemostatic factor, i.e. Fibrinogen was a strong predictor for Ischemic Heart Disease than cholesterol(12). The role of Fibrinogen concentration in the development of complications in DM was also suggested by Wilhelmsen *et al*, that Fibrinogen was a risk factor for stroke and Myocardial Infarction. The same findings were also reported by the Framingham study (12,13). Various studies suggest that hyperfibrinogeneamia may be one of the important missing links in the pathogenesis of diabetic vascular disease. In this study, the plasma Fibrinogen is increased in DM The increase in plasma Fibrinogen can be stated in the following hypothetical pathway (14).

Fibrinogen plays an important role in haemostasis. It participates in both the primary and secondary haemostatic process. In addition, Fibrinogen participates in the regulation of blood viscosity and in acute-phase reactions of infection, injury or trauma (15). In view of this diversity of action it is aberrant plasma Fibrinogen levels might influence the function of the circulatory system at any of several sites, including the cerebral circulation. Fibrinogen, in particular, has the potential to participate in many pathological processes. Thus, high levels of Fibrinogen may predispose to thrombosis by producing a hypercoagulable state; accelerate atherogenesis and the development of atherosclerosis; and reduce blood flow through rheological effects (e.g. high plasma viscosity, erythrocyte aggregation and leucocyte activation). Hyperviscosity has been shown to be an important component of microcirculatory disorder in DM (12).

The hypothetical pathways that leads to increased plasma Fibrinogen level in DM: Hyperglycaemia and insulin-resistance, and the consequent oxidative stress, may give rise to increased thrombin formation. This process causes increased production of prothrombin fragments (F1+2) and increased turnover of Fibrinogen, with increased production of fibrin and consequently increased release of fragment D. Both F1 +2 and fragment D regulate the production of Fibrinogen in the liver; increased release of them into the circulation may produce an increase in circulating Fibrinogen. This suggests that a high level of Fibrinogen in plasma might be a risk marker for cardiovascular disease because it reflects increased thrombin formation and therefore a greater probability that a thrombotic event will occur(16,17).

In our study, the parameter HbA1c were compared between the 3 groups, which was found to be increased in the group 2. Moreover, recently a similar association has been described between HbA1c and plasma Fibrinogen. As HbA1c increases the Fibrinogen values were also increased. Moreover, recently a similar association has been described between HbA1c and plasma Fibrinogen by Vanninen E.*et al*(18). In this study, hsCRP was determined among all the 3 groups, as a marker of inflammatory status. It is found that hsCRP is increased in group 2 which is statistically significant ($p < 0.001$). As DM is an inflammatory state, hsCRP is increased in group 2. In our study we found a positive correlation of hsCRP with plasma Fibrinogen. Pasceri *et al* have shown that CRP induces adhesion molecule expression in human endothelial cells and directly influences atherosclerosis. Hashimoto *et al* found that C-reactive protein is an independent predictor of the rate of increase of carotid atherosclerosis. Fibrinogen may also be considered as a marker of advanced atherosclerosis, and also binds to platelets contributing to platelet aggregation and fibrin formation (13,19–21).

In our study the FBS and HbA1c values were increased in group 2 when compared to other groups indicating uncontrolled glycemic status. Jones *et al*., found that shortened Fibrinogen survival was reversible by correction of hyperglycaemia. Therefore, it is possible that acute fluctuations in glycaemia play an important role in thrombin activation (14,22,23). The uric acid levels were increased in group 2 than in group 3 and group 1. Lipid metabolic disorder is usually coupled with hyperuricemia, possibly because increasing lipoprotein esterase levels may decrease the clearance of UA. Otherwise, hyperuricemia may reduce TG Decomposition and increase TG levels by repressing lipoprotein lipase activity(24–26).

The association between insulin resistance, hyperuricemia and hypertriglyceridemia are complicated. This might be expected from the fact that uric acid production is linked to glycolysis and that glycolysis is controlled by insulin. Phosphoribosyl pyrophosphate (PPRP) is an important metabolite in this respect. Its availability depends on ribose-5-phosphate (R-5-P), the production of which is governed by glycolytic flux. Diversion of glycolytic intermediates toward R-5-P, PPRP, and uric acid will follow if there is diminished activity of GA3PDH (glyceraldehyde-3-phosphate dehydrogenase), which is regulated by insulin. Serum triglyceride concentrations may also increase, as might be expected from accumulation

of glycerol-3-phosphate. Thus, intrinsic defects in GA3PDH and a loss of its responsiveness to insulin, by causing accumulation of glycolytic intermediates, may explain the association between insulin resistance, hyperuricemia, and hypertriglyceridemia by Leyva *et al* (27)

Disturbance of lipid metabolism linked to insulin resistance may be the primary event in the development of IHD in type 2 diabetes. The relative insulin deficiency that occurs in type 2 DM impairs the action of lipoprotein lipase and leads to a characteristic atherogenic lipid pattern of elevated serum TGs, low serum HDL-C levels, and a preponderance of small, dense LDL particles(27).

The HDLc levels were increased in the group 1 than group 2 and group 3. HDL known to be good cholesterol was decreased in group 2 and group 3. HDL may provide cardiovascular protection by promoting reverse cholesterol transport from macrophages. The LDLc levels were decreased in the group 2 and 3 than in group 1, as they were on statins. Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for CVD. The VLDLc levels were increased in group 2 than in group 3 and 1. In DM subjects insulin fails to suppress synthesis of large VLDL particles. In addition, insulin resistance is associated with increased flow of free fatty acid to liver, and decreased clearance of VLDL particles, all of which increase VLDL concentration in plasma (28). TGL was increased in group 2 than in group 3 and group1. In this study, mean difference of TGL between the three groups were statistically significant. The glycaemic control is directly related to hypertriglyceridemia, higher the blood glucose higher the TGL level. Insulin plays a key role in triglyceride metabolism (29)(30). The increased flux of free fatty acids into the liver in the presence of adequate glycogen stores promotes triglycerides production. The liver responds to free fatty acid flux by triglyceridemia, which is typically observed in diabetes.

The findings in our study proves the relationship of Fibrinogen with vascular complications.so hyperfibrinogeneamia in type 2 diabetics along with other risk factors may be a major independent predictor of vascular complications. The study has its own limitation that if the Sample size was large the findings in the study could have been extrapolated to the general population. Study population with other causes of vascular ischemia (stroke, DVT) could have been included.

CONCLUSION

The study also suggests that fluctuations in glycaemia, as evidenced by increased HbA1c in group 2, can also have an impact on the plasma Fibrinogen levels. The prognostic significance of hyperfibrinogeneamia in DM can be determined only by prospective studies.

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