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Original Research Article

Association of plasma fibrinogen and development of complications in type 2 diabetes mellitus

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ABSTRACT

Background: Fibrinogen is a glycoprotein produced by the liver that plays a crucial role in blood clotting. Elevated levels of fibrinogen have been associated with an increased risk of cardio vascular disease, stroke and other chronic conditions. Several studies have investigated the relationship between fibrinogen and diabetes mellitus. Furthermore, fibrinogen has been suggested to play a role in pathogenesis of diabetes and its complications by promoting inflammation and endothelial dysfunction. The aim of the study was done to study association of fibrinogen levels and development of complications of diabetes mellitus.
Methods: A cross sectional observational study was conducted at medicine department of Dhiraj Hospital, Vadodara. Total of 114 diabetes mellitus patients were studied. The level of fibrinogen as well as presence of various risk factors like smoking, hypertension, obesity, dyslipidemia and different microvascular and macro-vascular complications were assessed. There were no conflict of interest.
Results: Of 114 patients smoking, overweight, hypertension, uncontrolled diabetes and dyslipidemia was reported in 54.4%, 30.7%, 41.2%, 28.1% and 60.5% respectively. Microvascular complication like retinopathy, nephropathy and neuropathy was reported in 34.2%, 40.4% and 21.1% patients respectively. Macrovascular complications like coronary artery disease and stroke was reported in 20.2% and 16.7% patients respectively. Average level of fibrinogen was found higher amongst diabetic patients with microvascular as well as macrovascular complications.
Conclusions: Serum fibrinogen level was found to be higher among patients with poor glycemic control, dyslipidemia, hypertension and higher BMI. A positive correlation was found between the level of fibrinogen and various complications of diabetes mellitus.

Keywords: Fibrinogen, Diabetes mellitus, Complications

INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disorder leading to poor glycemic control. Chronic hyperglycaemia contributes to initiation and occurrence of micro and macro vascular complications in DM.[1]

DM is linked with elevated fibrinogen, increased thromboxane A2, reduced platelet synthesis of nitric oxide, in addition to increased plasminogen activator inhibitor-1 (PAI-1) release causing inhibition of thrombolysis.[2]

Plasma fibrinogen is developed in the liver and following activation of the coagulation pathway is transformed to a fibrin monomer (by thrombin) which gradually attaches to neighbouring molecules through lateral aggregation, forming the blood clot.[3] Fibrinogen levels can be elevated

in individuals with diabetes, and this can contribute to the development of various complications associated with the disease.

Age, gender, smoking, alcohol consumption, body mass index (BMI), hypertension, dyslipidemia and glycemic control are various modifiable and non-modifiable determinants of level of fibrinogen.[4] The normal range of fibrinogen in the blood is 200-400 mg/dl. Fibrinogen is a key coagulation factor playing major role in final common coagulation pathway. The physiologic importance of fibrinogen is demonstrated by the bleeding diathesis related with a-fibrinogenemia and dysfibrinogenemias.[5-7] Fibrinogen has an important role in atherosclerosis and thrombosis related events like haemostasis, inflammation, fibrinolysis, proliferation of smooth muscle, and platelet aggregation. However, it's association with the process of atherosclerosis is still controversial regarding its causation.

The formation of fibrinogen rises by about 20 times during strong inflammatory triggers, as it is an acute inflammatory phase reactant.[8,9] During acute inflammation, interleukin-6 acts as a key mediator for increased fibrinogen synthesis.[10] Moreover elevated fibrinogen level may be considered as a marker of low grade inflammation in vascular disease. Fibrinogen and fibrin degradation products have a role in regulation of the cytokine mediated action and leukocyte-endothelial interactions which may be responsible for the enhanced inflammatory reaction in vascular disease lesions.[11]

The insulin resistance syndrome and type 2 DM are the important and common conditions reported associated with both increased level of fibrinogen and cardiovascular morbidities.[12,13] The exact mechanisms responsible for hyperfibrinogenemia in type 2 DM have not been explained yet. The low grade inflammatory reaction, hyper-insulinemia and hypoalbuminemia due to albuminuria are some suggested mechanisms for hyperfibrinogenemia.[14,15] Zanetti et al and Schrem et al have recommended some mechanisms responsible for the hyperfibrinogenemia in diabetes patients.[15,16] Hypoalbuminemia following albuminuria in diabetes patients leads to reduced plasma oncotic pressure; in turn stimulating hepatic protein synthesis, including fibrinogen which is finally responsible for cardiovascular morbidities.[16]

Multiple factors affect fibrinogen levels. The level of fibrinogen increases with age, body mass index, smoking, post-menopausal state, raised LDL cholesterol, lipoprotein A and leukocyte count. It decreases with physical activity, moderate alcohol intake, increased HDL cholesterol and with hormone replacement therapy.[17-19]

High level of fibrinogen were observed in non-alcoholics or who consume alcohol more than 60 g per day. There is a U shaped relationship with alcohol which is stronger in men than in women.[18]

Interventions to lower fibrinogen level

Lifestyle modifications like smoking cessation, weight reduction, stress management, regular physical activity and moderate alcohol consumption can change the level of fibrinogen. Among all these lifestyle modifications, cessation of smoking is most effective. Moderate alcohol consumption also causes reduction in fibrinogen level.

Fibrates i. e.; bezafibrate, and anti-platelet drug ticlopidine are the oral fibrinogen reducing medications. The efficacy of the bezafibrate and ticlopidine is 40% and 16% respectively. Intravenous fibrinolytic agents and heparin are also effective in lowering fibrinogen dramatically; however, these drugs are not indicated for this reason alone and needs further research. Low dose aspirin medication has no significant effect on fibrinogen level.

Eriksson et al found evidence supporting positive effect of hormone replacement therapy in reducing the level of fibrinogen.[20] Various antihypertensive medications have shown diverse effects on fibrinogen and lipid profile, which affect the overall risk of the patients. Patients who were on 'lipid-neutral' (ACE-I, Ca-blocker, angiotensin-II blocker) or 'lipid friendly' (alpha-blocker) anti-hypertensive medications had significantly reduced level of fibrinogen, when compared with those who were on 'lipid hostile' drugs (beta-blocker, thiazide diuretic). The level of lipoprotein A is found raised among patients with DM especially among those with the poorer control of glycemic status. Lp(a) has a key role in diabetes and its micro as well as macro vascular complications by reducing fibrinolysis and thus raising the level of fibrinogen.[21]

METHODS

A cross sectional observational study was conducted at Medicine department of Dhiraj Hospital, S. B. K. S., Medical Institute and Research Centre, Sumandeep Vidyapeeth University, Piparia, Waghodia, Vadodara. The study participants were newly diagnosed as well as known cases of DM presenting in outpatient department. The study was started after taking clearance from institutional ethics committee and was conducted from March 2020 to August 2021. The patients were included in the study after taking the written informed consent.

Inclusion criteria

Patients with type 2 DM (newly diagnosed or known cases, with or without microvascular or macrovascular complications) were included.

Exclusion criteria

Patients with coagulation abnormalities/anticoagulant therapy; presence of features of active infection/inflammation like fever, diabetic foot ulcer, urinary tract infection; women on hormonal replacement therapy; and any person not willing to participate in study

were excluded. Criteria and case definition for classifying the patients as DM was as per ADA guidelines and were evaluated for micro and macrovascular complications.

The data was collected and studied as per standard statistical protocols using Epi Info software version 16.

RESULTS

The baseline characteristics of the study population are as in Table 1.

There were 114 patients in our study, of which 62.3% were male and 37.7% were female. The average age was 55.1±7.94 and average BMI was 23.4±3.5. Among them, 62 (54.4%) patients were smokers; 47 (41.2%) patients were hypertensive; 32 (28.1%) patients had poor glycemic control (HbA1c>7.9%) while 31 (27.2%) patients had good glycemic control (HbA1c <7.0%) and 51 (44.7%) patients had fair glycemic control (HbA1c 7.0-7.9%). The mean TC, HDL and fibrinogen level was 208.7±20.7 mg/dl, 48.4±3.6 mg/dl and 441.9±31.1 mg/dl respectively, and 69 (60.5%) patients had dyslipidemia.

Microvascular complications i.e. retinopathy, nephropathy and neuropathy was reported in 39 (34.2%), 46 (40.4%) and 24 (21.1%) patients respectively whereas macrovascular complications i. e.; coronary artery disease and stroke were reported in 23 (20.2%) and 19 (16.7%) patients respectively.

The mean fibrinogen level was 458.20±22.90 mg/dl among overweight/obese patients, 441±24.9 mg/dl among patients with the normal BMI and 368.9±12.1 mg/dl among underweight patients. The average level of fibrinogen was found increasing with increase in BMI of the patients. The difference in average of fibrinogen among these three groups was found to be statistically significant. The mean fibrinogen level was higher among patients who had poor glycemic control (465.4±20.9 mg/dl) as compared to patients who had fair (442.5±24.7 mg/dl) or good (416.5±30.3 mg/dl) glycemic control which was statistically significant (p value<0.0001). The average fibrinogen level was higher among patients with dyslipidemia (456.2±22.2 mg/dl) and this difference was statistically significant (p value<0.0001). Although the mean fibrinogen level was found higher among hypertensive patients too (464.3±20.9 mg/dl), but it was not statistically significant. The above table shows average level of fibrinogen in patients with microvascular and macrovascular complications in our study. The average level of the fibrinogen was 439.7 mg/dl, 449.8 mg/dl and 458.0 mg/dl among patients with retinopathy, nephropathy and neuropathy respectively. The average level of the fibrinogen was 469.6 mg/dl and 477.9 mg/dl among patients with coronary artery disease and stroke respectively.

The average fibrinogen level was higher among patients with nephropathy (449.8±25.7 mg/dl) and patients with CAD (469.6±18.5 mg/dl) and this difference was statistically significant (p value=0.04). Likewise, the average fibrinogen level was higher among patients with neuropathy (458.0±24.2 mg/dl) and in patients with stroke (477.9±19.3 mg/dl) but this difference was not found statistically significant. Also, the average fibrinogen level was lower among patients with retinopathy (439.7±31.3 mg/dl) and this difference too was not statistically significant.

Table 1: Baseline characters.

Characteristics		N	%
Mean age (years)	55.1±7.9		
Sex	Male	71	62.3
	Female	43	37.7
BMI	High	35	30.7
	Normal	72	63.2
	Low	7	6.1
Smoker	Yes	62	54.4
	No	52	45.6
Hypertension	Yes	47	41.2
	No	67	58.8
HbA1c	Poor	32	28.1
	Fair	51	44.7
	Good	31	37.2
Dyslipidemia	Yes	69	60.5
	No	45	39.5

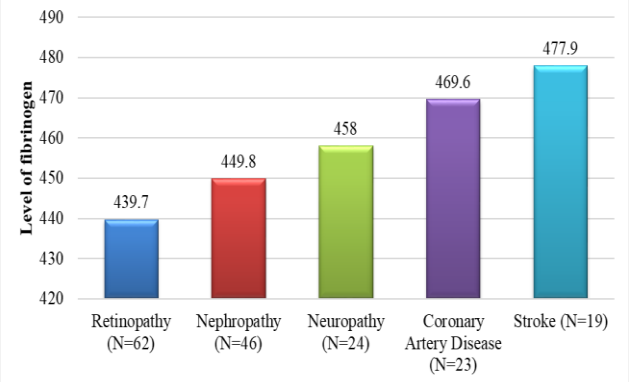

Figure 1: Level of fibrinogen in patients with microvascular and macrovascular complication.

DISCUSSION

Fibrinogen levels can be influenced by various factors, such as age, gender, smoking, and obesity. It can also be found elevated in conditions such as diabetes, cardiovascular disease, and inflammatory disorders. Elevated fibrinogen levels have been associated with an increased risk of various health conditions, including cardiovascular disease, stroke, deep vein thrombosis, and pulmonary embolism.

The present study was conducted to study the importance of measuring plasma fibrinogen in patients with type 2 DM and to study its correlation with parameters like age,

sex, smoking, glycemic control and dyslipidemia. Association of fibrinogen was also studied with various microvascular and macrovascular complications. The mean age of the studied population was 55.1 years, of which 62.3% were male.

In our study higher level of fibrinogen was found in obese/overweight patients and the association was highly significant. This was similar to other studies done by Kamath et al, Bembde et al and Ganda OP et al.[22-24]

The prevalence of hypertension was 47% in our study and the level of fibrinogen was significantly higher among hypertensive patients which was similar to studies conducted by Ganda et al and Bembde et al.[23,24] There was a positive correlation between level of fibrinogen and poor glycemic control which was comparable to a study conducted by Bembde et al.[23]

The average fibrinogen level was higher among patients with dyslipidemia in our study which was similar to a study done by Bembde et al.[23] In the present study coronary artery disease and stroke was reported in 20% and 16% patients respectively. The fibrinogen levels were found to be higher in both CAD and stroke, although the statically significant difference was noted only in patients of CAD. Hong et al found that fibrinogen level appeared to be an independent risk factor for the severity of CAD in diabetic patients.[25]

The prevalence of diabetic retinopathy was 34.2% and in the present study which was a little lower than the studies conducted by Costa et al and Isoma et all.[26,27] Although the neuropathy was found in 21% of patients who had elevated levels of fibrinogen, this association was not found statistically significant as in retinopathy. Diabetic nephropathy was found in 40.3% of study population and the average fibrinogen level was 449.8±25.7 mg/dl which was statistically significantly higher. Similar results were obtained in a study conducted by Zhang et al where they found that the elevated serum levels of fibrinogen were associated with diabetic ESRD in patients with type 2 DM.[28]

Based on our findings we may conclude that elevated levels of fibrinogen have been linked to an increased risk of developing diabetes and its complications, although further research is needed to better understand the underlying mechanisms of this association.

Limitations

The study was a cross sectional, small scale study which did not have a comparison group. Larger, multi centric randomised controlled trials are needed for better understanding the association.

CONCLUSION

Measurement of fibrinogen level alongside other investigations like lipid profile can help the clinicians to better stratify the risk for development of various complications of DM.

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