Journal of Pathology of Nepal (2020) Vol. **10**, 1746 - 1750

Journal of
PATHOLOGY
of Nepal
www.acpnepal.com

Original Article

A study of correlation of plasma fibrinogen levels with glycemic status in type 2 Diabetes Mellitus patients

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Keywords:

Complications;
Glycated hemoglobin;
Plasma fibrinogen;
Type 2 diabetes mellitus;

ABSTRACT

Background: Plasma fibrinogen is an indicator of inflammation and endothelial dysfunction has been described as an independent risk factor for cardiovascular morbidity in type 2 Diabetes mellitus patients. Poor glycemic control has been reported to be associated with hyperfibrinogenemia and its complications. This study was aimed to find a correlation of mean fibrinogen level with glycemic control in complicated and uncomplicated cases of Type 2 Diabetes mellitus.

Materials and Methods: One hundred eight known cases of Type 2 Diabetes mellitus aged ≥ 30 were included in our study of which 39 cases were uncomplicated and 69 cases were complicated Diabetes mellitus. Hundred of non-diabetic age and sex-matched controls were analyzed. Blood samples were collected in Ethylenediaminetetraacetic acid and citrate bulb for estimation of HbA1c and plasma fibrinogen level respectively.

Results: Mean fibrinogen level in complicated Type 2 Diabetes mellitus was high 450.43 ±108.51 mg/dl as compared to uncomplicated cases 372.30±123.78 mg/dl (p=0.0001). Mean HbA1c in total Diabetes mellitus cases was 8.02±1.88 mg/dl with a range of 5.50-14.50 mg/dl. A positive correlation was found between HbA1c and mean fibrinogen level (r=0.782, p= 0.001) in type 2 Diabetes mellitus. Duration of diabetes in years showed a significant correlation with mean fibrinogen levels (r=0.295, p=0.002).

Conclusions: Plasma fibrinogen level was significantly associated with glycemic control (HbA1c) and duration of Diabetes mellitus in years. Thus, lowering plasma fibrinogen levels could be an important approach to the prevention of cardiovascular complications in diabetics.

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Received : May 1st 2020 ; **Accepted** : September 22nd 2020

Citation: Ghongade PV, Atram MA, Shivkumar VB. A study of correlation of plasma fibrinogen levels with glycemic status in type 2 Diabetes Mellitus patients. J Pathol Nep 2020;10: :1746-50. DOI: 10.3126/jpn.v10i2.28706

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia and disturbances in carbohydrates, fats, and protein metabolism.[1] Type 2 DM which is characterized by peripheral insulin resistance accounts for more than 90% of the global diabetic population.1 The global prevalence of DM in 2019 is estimated to be 9.3%, increasing to 10.2% by 2030.[2]

Also, the prevalence is higher in developed countries (10.4%) and urban areas (10.8%) than in developing countries (4.0%) and rural (7.2%) populations.[2]

DM is a hypercoagulable state with 75% of deaths due to cardiovascular diseases as a result of thrombotic complications.[3] Fibrinogen is an important constituent of the coagulation cascade and an important determinant of blood viscosity, platelet aggregation, and thrombus formation. Increased plasma levels of fibrinogen have been reported in patients of Type 2 DM.[4]. Plasma fibrinogen itself is determined by several modifiable and non-modifiable determinants like age, sex, smoking, hypertension, HbA1c, etc. So increased attention is needed to understand the disordered hemostatic mechanism in diabetes.[5]

Hence this study is aimed to evaluate the correlation of age, duration of type 2 DM with plasma fibrinogen levels, and glycated hemoglobin levels in patients with type 2 DM for early detection, monitoring, and appropriate management to reduce morbidity and mortality associated with type 2 DM.

MATERIALS AND METHODS

This is a cross-sectional study conducted at the Department of Pathology of tertiary care rural hospital from 2016 to 2018. This study was approved by the Institutional Ethical Committee and written informed consent was taken from all the patients. One hundred eight patients of DM, aged ≥30 years of either sex were included, of which 39 cases were without any complications and 69 cases had different microvascular and macrovascular complications. Clinical details of these patients along with socio-demographic data were recorded from the hospital information system. Hundred of non-diabetic age and sex-matched controls who did not have any chronic liver diseases, chronic kidney diseases, and any known coagulation disorder were selected. Appropriate control selection for the study was based on history, previous investigations were done in this hospital/outside, and also information from the medical record department.

Inclusion criteria were diagnosed cases of type 2 DM with or without related complications. The patients with a history of hypercoagulability, thromboembolism, inherited coagulation disorders, cancer, pregnancy, recent surgery, etc, and patients who were receiving standard anticoagulant treatment were excluded from the study. Venous blood samples of all the participants (patients and controls) were collected in Ethylenediaminetetraacetic acid and citrate bulb and were subjected for platelet count, fibrinogen level, and HbA1c. Fibrinogen level was estimated using the Clauss technique, with 'FIBROQUANT' test kit marketed by Tulip diagnostic on Behnk coagulometer.[6] HbA1c assay was done by particle enhanced immunoturbidimetric Methodology.[7]

Patient data were collected using a structural interview questionnaire and analyzed by the statistical package for social sciences (SPSS) program version 17. The Student's t-test was used to know the significant difference among the continuous variables between the 2 groups (DM type 2 patients in group 1 and controls in group 2). Pearson correlation (r) was done to assess the degree of association between variables in different groups. A p-value of <0.05 was considered statistically significant.

RESULTS

The study included 108 diagnosed patients of Type 2 DM of which 64 (59.3%) were males and 44 (40.7%) were females with a M: F ratio of 1.4:1. Analysis of clinical data and biochemical parameters using the t-test showed a significant correlation between variables such as age, duration of diabetes with HbA1c, and fibrinogen levels in patients with type 2 DM with and without complications.

Of the total 108 patients, 39 cases were Type 2 DM without complication and 69 cases were with different DM complications. The mean age of patients for uncomplicated Type 2 DM was 53.58±11.1years, for complicated DM was 57.85±11.33 years, and for the control group mean age was 54.33±12.13 years. Maximum patients of Type 2 DM with complications were found in the age group of 61-70 years (33.33%) followed by 51-60 years (30.43%).

Among 69 complicated cases of Type 2 DM, 13 (21.67%) cases were with myocardial infarction (MI), 10 (14.49%) cases with stroke, 11 cases (15.94%) with neuropathy, 11 cases (15.94%) with nephropathy, 14 cases (20.29%) with retinopathy, 10 cases (14.49%) with a gangrenous foot. The mean fibrinogen level in DM cases was found to be 422.22±119.77 mg/dl whereas in the control group it was 323.60±73.16 mg/dl (t=7.09 and p=0.0001). Also, the mean fibrinogen level in complicated Type 2 DM was high 450.43±108.51 mg/dl as compared to uncomplicated Type 2 DM cases 372.30±123.78 mg/dl (p=0.0001) (Table 1).

Based on HbA1c values patients were categorized into three groups 5.5–6.8% (good control), 6.9–7.6% (fair control) and >7.6 % (poor control). (Table 2). Mean HbA1c in type 2 total DM cases was found to be 8.02±1.88 mg/dl with a range of 5.50-14.50. In uncomplicated DM patients with

Table 1: Fibrinogen level in uncomplicated, complicated diabetic patients and control groups and comparison of mean fibrinogen values between groups

Group	Fibrinogen (mg/dl)	Mean fibrinogen value Comparison between groups	p-value
Uncomplicated	372.30±123.78	Uncomplicated Vs Control Group	0.022
Complicated	450.43±108.51	Complicated Vs Control Group	0.0001
DM Group(Total)	422.22±119.77	Uncomplicated Vs Complicated	0.0001
Control Group	323.60±73.16	DM Group Vs Control Group*	0.0001

DOI: 10.3126/jpn.v10i2.28706

Table 2: Comparison of glycemic control with plasma fibrinogen level in complicated and uncomplicated DM patients

DM groups	Good Control (HbA1c 5.5-6.8%)	Fair Control (HbA1c 6.9-7.6%)	Poor Control (HbA1c >7.7%)
Fibrinogen level in Uncomplicated DM patients	291.87±46.50	368.75±87.24	460±140.81
Fibrinogen level in complicated DM patients	334.37±48.43	397.69±59.32	514±89.14
t-value	2.53	0.90	1.69
p-value	0.017	0.37	0.096

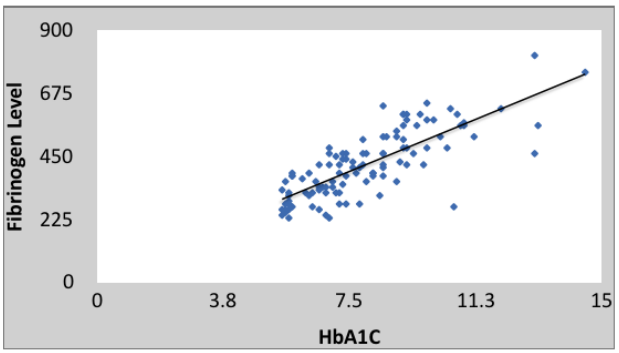

Figure 1: Correlation between HbA1c levels and mean fibrinogen values

good glycemic control, the mean fibrinogen level was 291.87±46.50 mg/dl in contrast to 334.37±48.43 mg/dl in complicated DM. (t= 2.53, p=0.017). Statistical correlation between HbA1c and mean fibrinogen level was found to be significant (r= 0.782, p= 0.001) (fig. 1)

On comparing the duration of diabetes with fibrinogen levels in patients with 10 to 15 years duration, the mean fibrinogen level was found to be a maximum of 502±142.68 mg/dl as compared with other groups. By using the Pearson coefficient test, a positive correlation was found between the duration of diabetes and mean fibrinogen levels (r=0.295, p=0.002). (Table 3)

DISCUSSION

DM is a major health problem whose burden is evident in developing countries like India as well.[8] It is among the top 10 causes of death and was estimated to have caused four million deaths in adults in 2017 worldwide.[9] In 2019 a total of 7.7 million people (20-79 years) from India are estimated to be living with diabetes. This number is expected to increase to 101 million (10.2%) in 2030 and 134 million (10.9%) in 2045. Currently, nearly half (50.1%) of people with diabetes do not even know that they have diabetes.[2] For the past two decades; irrespective of the type of DM, hemostatic factors especially fibrinogen has been considered as an independent risk factor for atherosclerosis and its complications like; MI, stroke, angina, etc.[10]

The mean age of patients for uncomplicated Type 2 DM was 53.58±11.1 years, for complicated DM was 57.85±11.33 years, and for the control group mean age was 54.33±12.13 years. Our findings are consistent with Agarwal C et al[11] who found 55.63±7.49 years as the mean age for patients with complicated type 2 DM. The youngest patient was 35 years old and the eldest was 80 years. The maximum numbers of patients were in the age group of 51-60 years (30.56%) followed by 61-70 years (29.63%) and 41-50 years (26.85%). These results are in agreement with a study by Bembde AS in which the maximum number of patients were in the age group 51–70 years (69%).[12]

The mean plasma fibrinogen level in total DM cases was found to be high 422.22±119.77 mg/dl in contrast to 323.60±73.16 mg/dl in the control group and this difference was statistically significant (p=0.0001). Our findings of high fibrinogen levels in cases of DM were consistent with Bembde AS[12], Sapkota B et al[13], and Gupta RK et al[14].

Also, the mean fibrinogen value was high 450.43±108.51 mg/dl in complicated cases as compared to 372.30 ±123.78 mg/dl in uncomplicated type 2 DM.[14,15] Thus, we concluded that levels of plasma fibrinogen are associated with the severity of type 2 DM.

Hyperfibrinogenemia in DM cases may be related to low-grade inflammation and elevated cytokines particularly

Table 3: Correlation of duration of DM in years with fibrinogen level

Duration	No.	Mean of fibrinogen (mg/dl)	Std. Deviation	Std. error	F-Value	P-Value	Correlation "r"
< 1 yrs	15	382.66	107.40	27.73	4.52	0.002	0.295 (+ve correlation)
1 to 5 years	39	377.69	104.01	16.65			
6 to 10 yrs	29	449.65	107.12	19.89			
11 to 15 yrs	15	502.00	118.62	37.51			
> 15 yrs	10	456.00	118.62	37.51			
Total	**108**	**422.22**	**119.77**	**11.52**			

DOI: 10.3126/jpn.v10i2.28706

interleukin-6 which stimulate hepatocytes to produce fibrinogen, representing an important link between inflammation and hypercoagulation.[16] Peripheral insulin resistance and hyperglycemia also have a direct impact on fibrinogen levels, whose concentrations are correlated with insulin and pro-insulin levels in healthy subjects also.[16]

In DM hyperfibrinogenemia is a result of a procoagulant state due to an increase in numbers of coagulation factors such as von-Willebrand factor, fibrinogen, plasminogen activator inhibitor 1, factor VII and thrombin antithrombin complexes particularly in association with microvascular and macrovascular complication and glycemic control.[17]

However, the mechanism by which fibrinogen increases the risk of cardiovascular complications is not fully understood. The proposed mechanisms by which hyperfibrinogenemia promote atherosclerosis and thrombus formation are increased plasma viscosity, inflammation and endothelial injury, induction of RBC and platelet aggregation, the formation of fibrinogen degradation products (FDPs) which bind low-density lipoprotein and sequester more fibrinogen and FDPs and fibrinogen stimulate smooth cell proliferation and migration.[12,17]

Besides, hyperfibrinogenemia was found to be associated with age, smoking, hypertension,

glycemic control, and duration of type 2 DM.18 The glycemic control affects fibrinogen levels, as relative deficiency of insulin in DM, results in differential protein synthesis i.e., a 29% decrease in albumin synthesis and a 50% increase in fibrinogen synthesis. Also, glycosylate fibrinogen is less susceptible to plasmin degradation.19

We also studied the correlation of duration of type 2 DM in years and fibrinogen level. Among the patient with DM with 10 to 15 years duration, the mean fibrinogen level was found to maximum 502±142.68 mg/dl as compared to patients with lesser duration of DM (p=0.002). Similar observations were made by Gupta RK et al.[14] However Kafue DR et al[15] did not find any significant association between the duration of diabetes in years and fibrinogen level.

In present study diabetic patients were categorized into three groups depending upon the HbA1c values i.e., 5.5–6.8% (good control), 6.9–7.6% (fair control), and >7.6% (poor control). Among 108 DM patients, 29.63 % of patients had good glycemic control, 19.44 % of patients had fair glycemic control and 50.93 % of the patients had poor glycemic control. A high number of diabetic patients (50.93%) with poor glycemic control in the present study might be due to poor dietary practices and lack of knowledge regarding the diet and exercise regimens that ought to be followed in diabetics.[20]

Mean HbA1c in Type 2 total DM cases was 8.02±1.88 % with a range of 5.50-14.50 and it correlated significantly with mean fibrinogen level 422.22±119.77 mg/dl (with a range of 230-810) in Type 2 total DM. Similar results have been observed by Bemde AS,12 Gupta RK et al,18 and Abdeurahman NM et al.[21]

In the present study, the mean HbA1c level in uncomplicated type 2 DM cases and complicated Type 2 DM cases were 7.41±1.78 % and 8.37±1.89% respectively, and this difference was statistically significant (p=0.001). The studies conducted by Mohan V et al[22] and Gupta RK et al[14] reported that the mean HbA1c level was high in patients with complicated DM. Mohan V et al[22] also concluded that the prevalence of both macrovascular and microvascular complications was high due to poor glycemic control.

Poor glycaemic control may lead to hypercoagulability because glucose causes a direct effect on the endothelium. Long-term hyperglycemia damages the endothelium by increasing glycosylation of proteins and lipids to form advanced glycation end products.23 Glycemic control in Indian diabetic patients is poor which has resulted in high morbidity and mortality associated with diabetic complications. However, in our study mean HbA1c value in total DM cases was 8.02±1.88 % which was lower than that in a study by Mohan V et al22 (9.2% in 20,554 patients of Type 2 DM). This difference is due to the small number of patients in our study. A significant positive correlation exists between age, duration of DM in years, plasma fibrinogen levels, and HbA1c.

CONCLUSIONS

Plasma fibrinogen levels are elevated in type 2 DM and this elevation was associated with poor glycemic control as evidenced by increased HbA1c levels. The other parameters which correlated with plasma fibrinogen levels were age and duration of DM in years. The patients in the 60-70 years of age group and having a history of DM for 10-15 years had higher fibrinogen levels compared to younger patients. Thus, lowering plasma fibrinogen levels could be an important approach to the prevention of cardiovascular complications in DM.

Conflict of interest: None

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