CORRELATION OF PLASMA FIBRINOGEN LEVELS WITH VARIABLES IN PATIENTS OF TYPE-II DIABETES MELLITUS WITH MICROVASCULAR COMPLICATIONS


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ABSTRACT

Background: Diabetes mellitus is considered as hypercoagulable state, where hypercoagulability of blood result in acceleration of atherosclerosis and diabetic microvascular complications. Three recognized diabetic microvascular complications include diabetic neuropathy, diabetic nephropathy and diabetic retinopathy. The aim of the present study was to evaluate association of plasma fibrinogen levels with other variables in patients with any of the three-recognized diabetic microvascular complications: diabetic neuropathy, diabetic retinopathy or diabetic nephropathy.

Methods: 104 patients of T2DM from in Medical unit-II and ophthalmology ward, Services Hospital, Lahore from April to October 2017 were included in present study. The patients were divided into two groups of 52 patients each. Group I comprised of Type 2 Diabetes Mellitus patients without any diabetic microvascular complications and Group II: Type 2 Diabetes Mellitus patients with any of three recognized diabetic microvascular complications: diabetic neuropathy, diabetic nephropathy and diabetic retinopathy (52 patients). Plasma fibrinogen levels, blood sugar fasting (BSF), HbA1c and BMI were evaluated in all patients.

Results: Spearman’s rank correlation coefficient, applied for measuring correlation of variables, showed statistically significant correlation (P < 0.05) of BSF r = 0.39; HbA1c r = 0.48 to plasma fibrinogen in patients with any of the three diabetic microvascular complications.

Conclusion: Higher fibrinogen levels (Clotting factor I) in plasma contribute significantly to establishment of microvascular complications in type-II diabetes mellitus patients. Fibrinogen levels were positively correlated with HbA1c and blood sugar fasting.

Key words: Plasma fibrinogen, microvascular complications, diabetes mellitus.

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INTRODUCTION

Diabetes mellitus (DM) is defined as a metabolic disorder due to multiple etiological factors and is featured by chronic hyperglycemia amalgamated with derangements of carbohydrate, protein and fat metabolisms causing long-term morbidity, dysfunction and failure of multiple body organs.1

Type II diabetes mellitus (T2DM), due to gradual loss of pancreatic β-Cell function, results in impaired secretion of insulin and increased requirement for insulin due to insulin resistance. Microvascular complications of DM include diabetic neuropathy, diabetic nephropathy and diabetic retinopathy, which are conditions manifesting from prolonged excess glucose levels in the small blood vessels supplying various body tissues2-5.

The pathophysiology of vascular complications
include hypercoagulable state and disturbed coagulation cascade in diabetes leading to extensive platelet aggregation and hence more clot formation.  

Many factors can affect plasma fibrinogen levels. It increases with an advancing age, body mass index (BMI), diabetes mellitus, tobacco smoking and in post-menopausal women. It declines with regular physical exercise, moderate alcohol consumption, high density lipoprotein cholesterol (HDL cholesterol) and with synthetic hormone therapy.  

Platelet aggregation seems to execute a major role in pathophysiology of hemostasis and thrombosis. This aggregation takes place through the interface of plasma fibrinogen with its receptor on platelets which is Glycoprotein IIb-IIIa complex. Fibrinogen is an active participant in a number of pathophysiological processes in the body including inflammation, thrombogenesis and atherogenesis. In the past few years, variation in hematological indices has been related to development of microvascular complications in diabetics. Few hematological factors such as blood viscosity and others are thought to participate significantly for microvascular complications in diabetics.  

The aim of our study was to evaluate an association of plasma fibrinogen with blood levels of glycated hemoglobin (HbA1c), fasting glucose and BMI in patients having any of the three diabetic microvascular complications.  

**METHODS**

This Cross-sectional study was conducted in Medical unit-ii and Ophthalmology ward, Services Hospital, Lahore and in the Institute of Molecular Biology and Biotechnology (IMBB), The University of Lahore from 15th April 2017 to 15th October 2017. Informed consent was taken from all patients recruited and their demographic data was recorded. The clinical parameters were also noted.  

The study included one hundred and four patients of Type-II Diabetes Mellitus with an age range 20-75 years. These patients were divided into two groups for comparison: Group I: Type-II Diabetes Mellitus (T2DM) patients without any microvascular complication (52 patients), Group II: Type 2 Diabetes Mellitus patients with any of the three recognized microvascular complications: Diabetic neuropathy, diabetic retinopathy or diabetic nephropathy (52 patients). Patients with any systemic illness altering the blood coagulability, inherited bleeding disorders, severe liver or cardiac failure or cancer, on oral contraceptive pills or who underwent surgical operation in last six months, or genetic disorders like hemoglobinopathies were excluded.  

Hematological and biochemical analysis were done by using Amax destiny plus fully automated coagulation analyzer by Trinity Biotech. Hemoglobin A1c (HbA1c), fasting plasma glucose were measured on chemistry analyzer (Hitachi 902 fully automated analyzer) manufactured by Roche Diagnostics Germany. Body mass index (BMI) was done by using the formula: weight measured in kilograms divided by height measured in square meter (kg/m2).  

The statistical analysis of the data was done by using Statistical Package for the Social Sciences; SPSS version 21 for windows (SPSS Inc., Chicago, IL, USA). Descriptive results were expressed as: mean ± SD (standard deviation). An independent samples t-test was utilized to compare means of variables. Spearman’s rank correlation coefficient was utilized for finding correlation between plasma fibrinogen levels and other clinical and laboratory parameters. P values < 0.05 were considered statistically significant.  

**RESULTS**

In our study, 104 T2DM patients were registered and were divided in two groups for comparison:

The mean age of the patients in Group I was 56.02 ± 8.52 years and mean age of the patients in Group II was 55.12 ± 9.91 years. The mean blood sugar fasting in Group I was 133.71 ± 29.80 and mean blood sugar fasting in Group II was 159.12 ± 37.12. Mean HbA1c in Group I was 6.73 ± 1.25 and mean HbA1c in Group II was 8.13 ± 1.50. Mean plasma fibrinogen in Group I was 295.98 ± 59.70 and mean fibrinogen level in Group II was 351 ± 62.78 .Mean BMI in Group I was 23.70 ± 3.96 and mean BMI in Group II was 22.98 ± 4.15 (Table 1).

An independent samples t-test revealed that there was a significant difference between the two groups statistically as regards plasma fibrinogen levels, blood sugar fasting and HbA1c (Table 1). According to Spearman’s rank correlation coefficient, following variables were statistically significantly correlated (P < 0.05) to plasma fibrinogen levels: Blood sugar fasting r = 0.59; HbA1c r = 0.79 (Table 2).

A bivariate Spearman’s rank correlation coefficient was used to examine whether there was a relationship between diabetic microvascular complications and plasma fibrinogen. Using a two-tailed 0.05 criterion, the results revealed a significant and positive relationship between the two variables [r (104) = 0.46, p <0.05]. The correlation was moderate in strength. Higher levels of plasma fibrinogen were associated with diabetic microvascular complications (Table 3).
Table 1: Age, BMI, Plasma Fibrinogen, Blood Glucose and HbA1c in patients with and without microvascular complications. The values are shown as mean ± Standard error of mean.

<table>
<thead>
<tr>
<th>TEST NAME</th>
<th>T2DM WITH MVC (n=52)</th>
<th>T2DM WITHOUT MVC (n=52)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.02±1.18</td>
<td>55.12±1.37</td>
<td>0.62</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>22.98±0.57</td>
<td>23.70±0.54</td>
<td>0.37</td>
</tr>
<tr>
<td>Plasma fibrinogen</td>
<td>351.08±8.70</td>
<td>295.98±8.27</td>
<td>.000</td>
</tr>
<tr>
<td>Blood sugar fasting</td>
<td>159.12±5.14</td>
<td>133.71±4.13</td>
<td>.000</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.13±0.20</td>
<td>6.73±0.17</td>
<td>.000</td>
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</tbody>
</table>

Independent samples T test: P < 0.05: Statistically significant

Table 2: Relationship between plasma fibrinogen and variables.

<table>
<thead>
<tr>
<th>Tested variables</th>
<th>N</th>
<th>Spearman’s rho correlation coefficient(r)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sugar fasting</td>
<td>104</td>
<td>.587</td>
<td>.000</td>
</tr>
<tr>
<td>HBA1c</td>
<td>104</td>
<td>.785</td>
<td>.000</td>
</tr>
<tr>
<td>BMI</td>
<td>104</td>
<td>.048</td>
<td>.628</td>
</tr>
<tr>
<td>Age</td>
<td>104</td>
<td>-.021</td>
<td>.83</td>
</tr>
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</table>

Statistical analysis by Spearman’s rank correlation coefficient

Table 3: Relationship between diabetic microvascular complications and plasma fibrinogen. Statistical analysis by bivariate Spearman’s rank correlation coefficient.

<table>
<thead>
<tr>
<th>Spearman’s rho</th>
<th>Groups</th>
<th>Correlation Coefficient</th>
<th>N</th>
<th>Fibrinogen</th>
<th>Correlation Coefficient</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>1.000</td>
<td>.458**</td>
<td>104</td>
<td>.000</td>
<td>.458**</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td></td>
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</table>

DISCUSSION

Diabetes Mellitus is one of the major causes of morbidity not only in developed but also in developing countries. Blood hypercoagulability in diabetes mellitus may result in acceleration of atherosclerosis and development of diabetic microvascular complications.12

One of the contributing factor to increased blood viscosity and hypercoagulability is elevated plasma fibrinogen levels which is considered as a cardinal risk factor for development of diabetic microvascular complications.13

Our study shows significantly elevated plasma fibrinogen level in T2DM patients with diabetic microvascular complications i.e. diabetic neuropathy, diabetic retinopathy or diabetic nephropathy as compared to T2DM patients without any diabetic microvascular complication.

The findings are consistent with study done by Mohan et al. that showed significantly increased serum fibrinogen level in 30 diabetic patients with complications as compared to controls.14 Neetha et al. studied plasma fibrinogen levels in 61 patients with diabetic retinopathy and compared them with those without diabetic retinopathy. The study pointed out that increased plasma fibrinogen level significantly contributes to the initiation and development of diabetic retinopathy.15

Aslam et al. concluded significant correlation of plasma fibrinogen levels with the three microvascular complications, suggesting that hyperfibrinogenemia leads to increased vascular complications in type 2 diabetes mellitus patients.16 Sarangi et al. point out the role of plasma fibrinogen in establishment of diabetic retinopathy.17

Our study showed significant correlation between plasma fibrinogen level and blood sugar fasting.
and HbA1C. Significant positive correlation exists between plasma fibrinogen levels and blood sugar fasting, and plasma fibrinogen and HbA1C. However, no significant correlation was found between plasma fibrinogen and body mass index in the study.

In diabetic microangiopathy there are numerous proposed phenomena explaining elevated fibrinogen level in patient of diabetes mellitus. Firstly it is thought to be linked with low grade inflammation. Exaggerated platelets, leukocytes activation and the presence of heterotypic aggregations have been documented in diabetic microangiopathy. Furthermore cytokines such as Interleukin-6 levels are increased in diabetes which is believed to stimulate liver cells, that synthesizes more fibrinogen, thus suggesting a crucial connection between inflammation and hypercoagulation. Insulin resistance is considered another important risk factor which leads to escalated fibrinogen hepatic production in patients of T2DM.

Gupta et al. found positive correlation of glycosylated hemoglobin (HbA1c) with fibrinogen level. Similarly Azad et al. found significant positive correlation of HbA1c with plasma fibrinogen level in patients with diabetic retinopathy.

Studies by Coban et al. and Mir et al. showed positive correlation between plasma fibrinogen level fasting blood sugar.

In our study, non-significant correlation was observed between plasma fibrinogen levels and BMI, which is in agreement with study by Lyer et al. but Bembde et al. showed significant correlation.

This study suggests that an important role of plasma fibrinogen in development of microvascular complications in diabetes mellitus patients. However, this study had several limitations. Firstly, the number of patients enrolled was relatively small. Secondly, the study design was cross-sectional.

Additional large-scale, prospective studies are needed to further evaluate the role of plasma fibrinogen levels in development of microvascular complications in diabetic patients. It is recommended based on this study that early drug therapy and management may be initiated to lower plasma fibrinogen levels in order to prevent initiation and progression of diabetic microvascular complications.

**CONCLUSION**

Higher fibrinogen levels (Clotting factor I) in plasma may contribute significantly to establishment of microvascular complications in type-II diabetes mellitus patients. Fibrinogen levels are positively correlated with HbA1c and blood sugar fasting.

**ACKNOWLEDGMENTS**

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