

# A STUDY ON SERUM FIBRINOGEN AS AN INDEPENDENT PREDICTOR OF MAJOR ADVERSE CARDIAC EVENTS IN KNOWN DIABETIC CORONARY ARTERY DISEASE PATIENTS

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## ABSTRACT

### BACKGROUND

Diabetes mellitus is one of the leading cause of morbidity and mortality worldwide. It is an important risk factor in the pathogenesis of Acute Coronary Syndrome. Fibrinogen, being an acute phase reactant is also a procoagulant. Hence its role in adverse cardiac events in diabetics and its prognostic value is currently the study of interest.

Aims and Objectives-

1. To determine the concentration of fibrinogen in Diabetic CAD patients.
2. To ascertain the prognostic value of serum fibrinogen in Diabetic patients.
3. To evaluate the relation between serum fibrinogen and other factors that cause adverse cardiac events.

### MATERIALS AND METHODS

This study we are undertaking is a cross sectional study conducted in Thanjavur Medical College, Thanjavur. The study population includes 50 patients with diabetes mellitus admitted in department of internal medicine with past history of CAD or with evidence of CAD. The study period is from June 2016 to December 2016 for a period of 6 months. Department of cardiology and biochemistry are the collaborating departments in this study.

### RESULTS

52% of the patients in this study suffered from MACE. MACE is more common among older patients. Mean serum fibrinogen levels was significantly higher in patients with longer duration of diabetes and poor glycaemic control. Serum fibrinogen plays an important role in the pathogenesis of vascular complications in diabetics. There is a positive correlation between major adverse cardiac events and fibrinogen levels.

### CONCLUSION

The study concludes that 52% of the patients suffered from MACE and there is no gender variation. MACE is more common among older patients. Longer the duration of diabetes and poor glycaemic control leads to severe MACE. Mean serum fibrinogen level has positive correlation with diabetic status of the patients. Increased serum fibrinogen level is associated with severity of MACE.

### KEYWORDS

Type 2 Diabetes, Serum Fibrinogen, MACE, CAHD.

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### BACKGROUND

Diabetes mellitus is a metabolic disorder of varied aetiology characterised by chronic hyperglycaemia and altered metabolism of carbohydrate, protein and fat leading to vascular syndrome affecting small and large sized blood vessels.

Fibrinogen possess significant risk for cardiovascular disorders.<sup>1</sup> Its positive relationship with BMI has been

established by a study, which showed decrease in fibrinogen level following low calorie healthy diet for 6 months.<sup>2</sup>

Poor glycaemic status are often associated with increased fibrinogen level and this is evidenced by observation of increased platelet activity in diabetes. This may be due to high fibrinogen level which cross bridges platelets.<sup>3</sup> Diabetes and fibrinogen causes significantly increased risk of atherosclerotic CAD.<sup>4</sup> Fibrinogen as a predictor of CAD has been established by a study conducted by Thompson and colleagues.<sup>5,6,7</sup>

Plaque rupture and thrombosis are the key components in ACS. Pathogenesis of these events are largely contributed by increased level of fibrinogen and C reactive protein.<sup>8</sup> A study by Emansh et al suggest a strong link between high plasma fibrinogen level and premature CAD.<sup>9</sup> Atheroembolic events is further accomplished by several studies showing strong link between fibrinogen level and Ischemic CVA<sup>10,11</sup>

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and peripheral vascular disease.<sup>12,13</sup> Fogart et al<sup>14</sup> established association between smoking and serum fibrinogen levels, it is high in smokers when compared to non-smokers. Hence the role of fibrinogen in predicting adverse cardiac effects in diabetics is studied extensively.

## MATERIALS AND METHODS

This study we are undertaking is a cross sectional study conducted in Thanjavur Medical College, Thanjavur. The study population includes a sum of 50 patients with diabetes mellitus admitted in department of internal medicine with past history of CAD or with evidence of CAD. The study period is from June 2016 to December 2016 for a period of 6 months. Department of cardiology and biochemistry are the collaborating departments in this study.

### Exclusion Criteria

#### Patients with

- Liver disease,
- Disseminated intravascular coagulation,
- Sepsis,
- History of Drug abuse like OCPs, Antifibrinolytics are excluded from the study.
- Pregnant women are excluded from the study.

Convenience sampling method was adapted as the sampling method. All patients were investigated with CBC, Blood sugar (Random, Fasting and post prandial), HbA1C, RFT, urine analysis, serum fibrinogen, ECG and ECHO. Recurrent angina, Congestive cardiac failure, Arrhythmias, Death are considered as the major adverse cardiac event in this study.

### Estimation of Serum Fibrinogen

#### Clauss Method

In the presence of excess of thrombin fibrinogen is transformed into fibrin and clot formation time is inversely proportional to the concentration of fibrinogen in the sample plasma. Venous blood collected in 3.8% sodium citrate in a ratio of 9 parts of blood to 1 part of anticoagulant.

### Procedure

To the fibro meter cup 0.2 ml of the diluted plasma sample is added. This is incubated for 1-3 minutes at 37° C. after incubation 0.1ml of thrombin reagent is added rapidly and

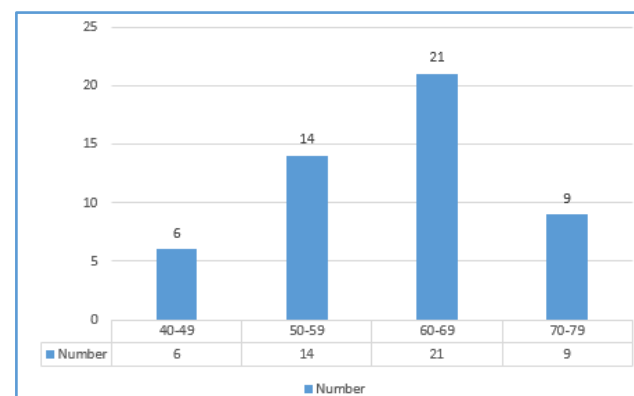
### Group wise Distribution of Study Population

	No. MACE	Recurrent Angina	Congestive Cardiac Failure	Arrhythmia	Death
Age	57.33	63.92	65.2	0	0
Duration of diabetes	11.4	13.54	15.55	0	0
FBS	139.78	187.85	213.68	0	0
PPBS	250.87	299.54	332.18	0	0
HbA1C	9.22	9.98	10.03	0	0
Serum Fibrinogen	306.07	344.08	426.32	0	0

**Table 1. Demographic Characteristics**

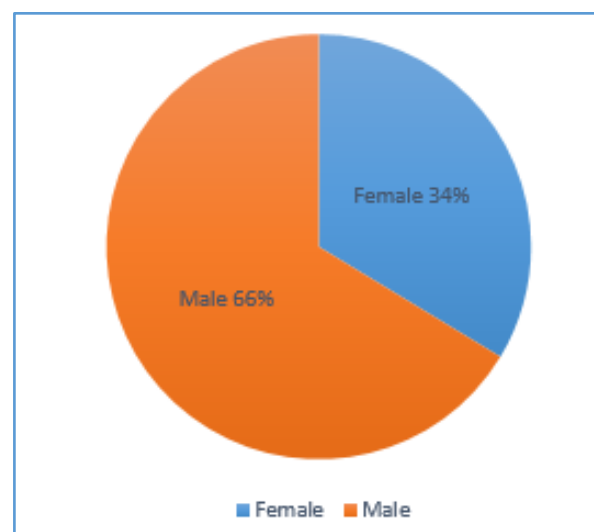
clotting time results recorded in seconds. Results evaluated and tabulated.

## RESULTS



**Figure 1. Age Distribution**

The total number of study subjects is 50. Among them age distribution ranges from 44-78 years. The majority of patients belong to 60-69 years of age (42%), followed by 50-59 age group (28%). (Fig. 1)



**Figure 2. Gender Distribution**

In our study, as far as the gender distribution is concerned, majority of the patients were males, about 66% are males and 34% are females. (Fig. 2)

The mean values have been matched against the major adverse cardiac events. In our study we did not have any patients with arrhythmia and there was no mortality. (Table 1).

<b>MACE</b>	<b>No. of Patients</b>	<b>Percentage</b>
No MACE	24	48
Recurrent angina	11	22
Congestive cardiac failure	15	30
<b>Total</b>	<b>50</b>	<b>100</b>

**Table 2. Prevalence of MACE**

The highest prevalence is that of patients who do not develop MACE (48%). This group is followed by congestive cardiac failure patients (30%), followed by recurrent angina (22%). This shows that the most prevalent adverse cardiac event is congestive cardiac failure. Table 2

	<b>40-49</b>	<b>50-59</b>	<b>60-69</b>	<b>70-79</b>	<b>Total</b>
No MACE	5	10	9	1	<b>24</b>
Recurrent angina	1	2	5	3	<b>11</b>
Congestive cardiac failure	0	2	7	5	<b>15</b>
<b>Total</b>	<b>6</b>	<b>14</b>	<b>20</b>	<b>9</b>	<b>50</b>

**Table 3. Relationship between MACE and Patient's Age**

From the above table MACE is more commonly found among patients in 60-69 years age group (20 patients), followed by 50-59 years (14 patients). It is also seen that among 9 patients in 70-79 age group, 8 have MACE. Though more number of MACE is present in 60-69 age group, about 88% of the patients in 70-79 age group have MACE. Table 3

	<b>Male</b>	<b>Female</b>	<b>Total</b>
No MACE	15 (30%)	6 (12%)	<b>24</b>
Recurrent angina	7 (14%)	4 (8%)	<b>11</b>
Congestive cardiac failure	11 (22%)	4 (8%)	<b>15</b>
<b>Total</b>	<b>33 (66%)</b>	<b>17 (34%)</b>	<b>50</b>

**Table 4. Relationship between MACE and Sex of the Patients**

There is no significant relation between gender variation and MACE. About 50% of the males and females have MACE. The numbers when statistically analysed, yielded a chi square value of 2.37 and a P value of 0.305 which is not significant. Table 4

	<b>5-10 yrs.</b>	<b>11-15 yrs.</b>	<b>&gt;15 yrs.</b>	<b>Total</b>
No MACE	6	14	4	24
Recurrent angina	2	3	6	11
Congestive cardiac failure	2	4	9	15
<b>Total</b>	<b>10</b>	<b>21</b>	<b>19</b>	<b>50</b>

**Table 5. Relationship between MACE and Duration of Diabetes**

RA and CCF group shows that majority of the patients developed it after 10 years of diabetes, it indicates that the more the duration of diabetes the more the chance of MACE. Chi square test was used to analyse and revealed a P value of 0.005 which is statistically significant. Table 5

<b>FBS</b>	<b>90-140</b>	<b>141-190</b>	<b>191-240</b>	<b>241-290</b>	<b>Total</b>
No MACE	14	10	0	0	24
Recurrent angina	0	5	6	0	11
Congestive cardiac failure	0	1	8	6	15
<b>Total</b>	<b>14</b>	<b>16</b>	<b>14</b>	<b>6</b>	<b>50</b>

**Table 6. Relationship Between MACE and Fasting Blood Sugar**

In RA group most patients belong to FBS 191-240 range. In CCF group most patients belong to FBS 191-240 group. However, the last FBS group 241-290 range had only 6 patients. (Table 6)

<b>PPBS</b>	<b>191-240</b>	<b>241-290</b>	<b>291-340</b>	<b>341-390</b>	<b>Total</b>
No MACE	11	8	5	0	24
Recurrent angina	1	4	6	0	11
Congestive cardiac failure	0	1	7	7	15
<b>Total</b>	<b>12</b>	<b>13</b>	<b>18</b>	<b>7</b>	<b>50</b>

**Table 7. MACE and Post Prandial Blood Sugar**

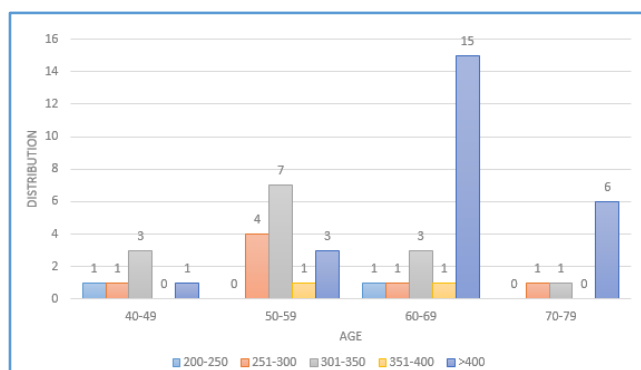
Majority of the patients comes in 291-340 group. CCF group shows equal presence of patients in 291-340 and 341-390 range. Table 7

#### *Relationship between MACE and Glycemic Control*

	<b>Well controlled HbA1C 6.2 – 8.3</b>	<b>Uncontrolled HbA1C &gt;8.3</b>	<b>Total</b>
No MACE	18	6	24
Recurrent angina	3	8	11
Congestive cardiac failure	0	15	15
<b>Total</b>	<b>21</b>	<b>29</b>	<b>50</b>

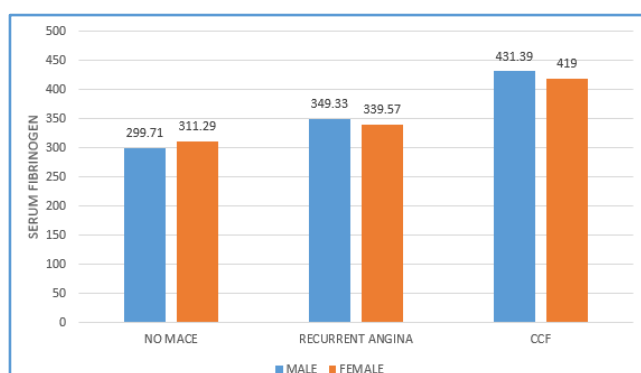
**Table 8. Relationship between MACE and Post Prandial Blood Sugar**

From this table, patients in recurrent angina and CCF group have uncontrolled diabetes. Their HbA1C was more than 8.3. It indicates that patients with uncontrolled diabetes have high chance of MACE. Chi-Square test revealed a P value of 0.0165 which is statistically significant. (Table 8)



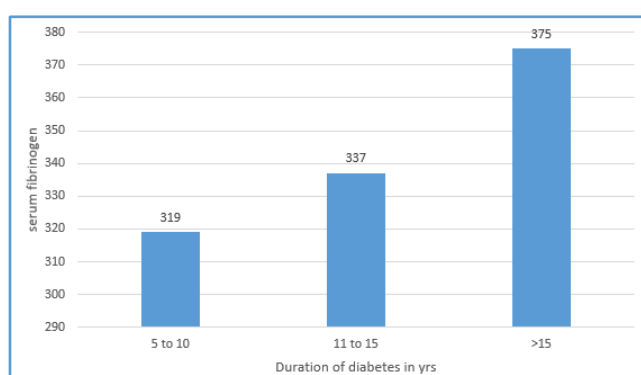
**Figure 3. Relation between Serum Fibrinogen and Age**

From this table, it is understandable that most of the patients with serum fibrinogen level more than 400 comes under 60-69 years of age. It signifies the impact of age in serum fibrinogen level. (Fig. 3)



**Figure 4. Relation between Serum Fibrinogen and Sex**

From this table, it is seen that there is no significant difference between both the sex in aspect to serum fibrinogen levels. It is not statistically significant. (Fig. 4)



**Figure 5. Relation between Serum Fibrinogen and Duration of DM**

From this table, it is seen that increase in serum fibrinogen is directly proportional to duration of diabetes. Chi square test yield a P value of <0.01 which is statistically significant. (Fig. 5)

	Well controlled HbA1c 6.2-8.3	Uncontrolled HbA1c >8.3
Mean fibrinogen level	315.06	354.10
No. of patients	21(42%)	29(58%)

**Table 9. Relation between Fibrinogen and Glycaemic Control**

From this table mean fibrinogen level is higher in patients with uncontrolled diabetes. P value is <0.01 which is statistically significant. (Table 9)

MACE	No. Of Patients	Mean Fibrinogen Level
No MACE	24	306.07
Recurrent Angina	11	344.08
Congestive Cardiac Failure	15	426.32

**Table 10. Relationship between Serum Fibrinogen and MACE**

From this table, serum fibrinogen levels are comparatively higher in CCF group than recurrent angina group which is higher than No MACE group. The results are statistically significant with P value of <0.001. (Table 10)

## DISCUSSION

The present study, which is cross-sectional in design, has a sample size of 50 patients. Among them 26 patients had Major Adverse Cardiac Events (MACE), 11 had recurrent angina, 15 had congestive cardiac failure (Table 2). This shows that the most prevalent adverse cardiac event is congestive cardiac failure. In our study we did not have any patients with arrhythmia and there was no mortality. In this study the severity of MACE increased with increasing age (Table 3). Though more number of MACE is present in 60-69 age group, about 88% of the patients in 70-79 age group have MACE.

In this study, there is no significant gender variation in MACE (Table 4). The numbers when statistically analysed, yielded a chi square value of 2.37 and a P value of 0.305 which is not significant. RA and CCF group shows that majority of the patients developed it after 10 years of diabetes, it indicates that the more the duration of diabetes the more the chance of MACE. Chi square test was used to analyse and revealed a P value of 0.005 which is statistically significant (Table 5). There is also a significant increase in severity of MACE with increasing values of FBS and PPBS (Table. 6 & 7). Patients with poor glycaemic control are at increased risk of MACE (Table. 8). Chi-Square test revealed a P value of 0.0165 which is statistically significant.

In our study mean serum fibrinogen correlates with the severity of diabetes. Serum fibrinogen level increases with increase in age (Fig. 3). Fibrinogen level is high when duration of diabetes is more than 15 years leading to vascular complications (Fig. 4). Since fibrinogen is a pro-coagulant there is a positive correlation between MACE and serum fibrinogen level (Fig. 5). Chi square test yield a P value of <0.01 which is statistically significant. With this study we can say that fibrinogen may be involved in increased cardiovascular risk of patients with diabetes.

**CONCLUSION**

*The study concludes that*

- 52% of the patients suffered from MACE
- There is no gender variation
- MACE is more common among older patients
- Longer the duration of diabetes and poor glycaemic control leads to severe MACE.
- Mean serum fibrinogen level has positive correlation with diabetic status of the patients.
- Increased serum fibrinogen level is associated with severity of MACE.
- Serum fibrinogen plays an important role in the pathogenesis of vascular complications in diabetics.

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