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A Study to Evaluate Correlation of C-Reactive Protein and Glycosylated Haemoglobin in Patients of Diabetes Suffering from Acute Coronary Syndrome

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Abstract

Incidence of diabetes is increasing substantially worldwide. Cardiovascular disease is most prevalent cause of mortality and morbidity in diabetic populations. Cardiovascular risk factor including obesity, hypertension, dyslipidemia are common in patients with diabetes mellitus particularly with those of type 2 diabetes. Atherosclerosis has been described as an inflammatory disease. **Aim:** Study **t**o evaluate correlation of C-Reactive Protein and Glycosylated Haemoglobin in Patients of Diabetes Suffering from Acute Coronary Syndrome. **Material and Methods:** A descriptive study after satisfying criteria was conducted in 115 patients in medicine department of a medical college and tertiary care hospital over a period of two years that included patients of diabetes suffering from acute coronary syndrome in the age group of 30 to 70 years. Evaluation and correlation was done by clinical profile. **Results:** Majority of patients were elderly age group of male of 51 to 60 yrs having mean BMI of 24 kg/m^2. CRP level of >3 mg/dl was found in 77.39% and majority of patients had HbA1C >7%. CRP and HbA1C were significantly correlated ($p<0.05$). Majority of patients with elevated CRP were found in with killip class I. But CRP and killip classification were not significantly correlated in our study. **Conclusion:** Elevated C Reactive Protein and Glycosylated Haemoglobin are better correlated as poor prognostic marker for cardiovascular event in patients of diabetes suffering from acute coronary syndrome.

Keywords: CAD, Cholesterol, CRP, Diabetes, HbA1c

1. Introduction

Incidence of diabetes is increasing substantially worldwide[1]. Cardiovascular disease is most prevalent cause of mortality and morbidity in diabetic populations[2]. Cardiovascular risk factor including obesity, hypertension, dyslipidemia are common in patients with diabetes mellitus particularly with those of type 2 diabetes[2]. Atherosclerosis has been described as an inflammatory disease[2]. In this study elevated CRP was employed as potent risk indicator for CHD. Elevated HbA1C is an established predictor for developing atherosclerosis beyond the risk associated with diagnosed diabetes[3,4].

Hence present study was done at our tertiary care centre to assess the clinical profile of diabetic patients who presented with acute coronary syndrome and to look for correlation of on admission blood sugar level, CRP and HbA1c with short term clinical severity in same patients.

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2. Aim

- To study the clinical profile of diabetic patients who present with Acute Coronary Syndrome (ACS) for the first time.
- To detect correlation between levels of C-reactive in patients of Acute Coronary Syndrome.
- To find correlation between levels Glycosylated Haemoglobin (HbA_{1c}) in patients of Acute Coronary Syndrome.

3. Materials and Methods

Study Area: Department of General Medicine in a tertiary care hospital.

Study Population: All patients presenting with Acute Coronary Syndrome with known case of diabetes fulfilling inclusion and exclusion criteria.

Duration of Study: 2 years, August 2016 to December 2018.

Study Design: Hospital based descriptive study. It was descriptive study conducted in 115 patients in Medicine Department of a Medical College and Tertiary Care Hospital over a period of two years that included patients of diabetes suffering from acute coronary syndrome in the age group of 30 to 70 years. Evaluation and correlation was done by clinical profile, investigations-CRP, HbA1C, Cardiac enzyme, 2dEcho.

4. Methodology

Patients who were known diabetics detected for the first time with acute coronary syndrome presenting in Outpatient Department of General Medicine or Emergency Department of Tertiary Care Hospital were studied. Study period was 2 years between August 2016 to December 2018. This was descriptive case study where all patients in adult age group were studied. Those patients satisfying inclusion and exclusion criteria were included in the study. All the patients were explained about the procedure, purpose of study, informed consents were taken.

5. Diagnostic Criteria for Diabetes Mellitus

- Symptoms of diabetes plus random blood glucose > 200 mg/dl
- Fasting => 126 mg/dl (7.0 mmol/l)
- HbA1c level >6.5%

6. C-Reactive Protein Estimation

C-Reactive Protein is measured by collecting venous sample and using Turbidimetric immunoassay for C-reactive protein. Based on the review of the published data, the CDC and American Heart Association (AHA) have recommended following guidelines for assessment of cardiovascular disease risk:

(Normal - 0 to 0.6 mg/dl)

Low Risk: CRP level of 1mg /dl or lower.

Moderate Risk: CRP level of 1-3 mg/dl.

High Risk: CRP level of greater than 3 mg/dl.

CPR level greater than 10 mg/dl may suggest acute coronary process.

Glycosylated Haemoglobin was measured with the help of high performance liquid chromatography. Standard 12 lead ECG machine (Global) is used for assessment of patients. Cardiac Biomarker CKMB (0 to 4.3 ng/ml) and serum Troponin T (0 to 0.4 ng/ml) was performed using standard card test.

Grading of Clinical severity was based on killip classification[5]:

Class I: No congestive heart failure.

Class II: Mild congestive heart failure, rales.s3, congestion on chest radiograph.

Class III: Pulmonary oedema.

Class IV: Cardiogenic shock.

6.1 Inclusion Criteria

Patients who are diagnosed to have acute coronary syndrome based on clinical evaluation of their history, physical examination, an electrocardiogram and cardiac biomarkers (serum CK MB (0 to 4.3 ng/ml) and serum Troponin T (0 to 0.4 ng/ml) and who are known diabetics.

6.2 Exclusion Criteria

- Patients with previous history of acute coronary syndrome or ECG suggestive old myocardial infarction.
- Patients with chronic coronary artery disease and patients with documented evidence of extra cardiac atherosclerosis like ischemic stroke, peripheral vascular disease.

- Patients with cardiac valve disease and life threatening arrhythmias.
- Patients on Aspirin, Statins and NSAIDS.
- Patients with acute or chronic kidney disease.
- Serum creatinine more than 1.2 mg/dl.
- Blood urea more than 40 mg/dl,
- Patients with acute or chronic liver disease
  Serum Bilirubin Total more than 1 mg/dl.
  Serum SGOT more 40 IU/L
  Serum SGPT more than 40 IU/L.
- Patients with febrile disorders (Body temperature more than 37.5 degrees Celsius).
- Patients with known case of malignancy.

6.3 Statistical Analysis

Quantitative data was presented with the help of Mean and Standard deviation. Qualitative data was presented with the help of frequency and percentage table. Results were graphically represented where deemed necessary. Appropriate statistical software, including but not restricted to MS-Excel. SPSS version 20 was used for statistical analysis. Graphical representation was done in MS-Excel 2010.

6.4 Association of Glycosylated Haemoglobin (HbA1c) and C-Reactive Protein (CRP) Values Inpatients

It was observed that significantly higher number of patients with elevated CRP values had HbA1c values in the range of 7-9%. Association of Glycosylated Haemoglobin (HbA1c) and C-Reactive Protein (CRP) values were associated in these patients ($p<0.05$).

7. Results

7.1 Age

Majority of the patients (33.1%) were in the age group of 51-60 years followed by 22.6% in the age group of 41-50 years, 20% in the age group of 61-70 years, 15.6% in the age group of 71-80 years and 8.7% in the age group of 31-40 years. The mean age of the patients was 56.13 ± 12.10 years. Majority of patients belong to sixth decade of life thus advance age is a non modifiable risk factor for coronary artery disease was proved in our study.

7.2 Male and Female

82 (71.3%) patients were male while 33 (28.7%) patients were female in our study group. Majority of patients with ACS in our study had male preponderance.

7.3 BMI

83 (72.2%) patients were in normal range of BMI (18.5 to 24.9 kg/m^2), 20 (17.4%) and 12 (10.4%) patients were overweight (25 to 29.9 kg/m^2) and obese (more than 30 kg/m^2) respectively. The mean BMI of patients was 24.57 ± 3.10 kg/m^2. Although obesity is common in type 2 Diabetes and obesity is a modifiable risk factor for coronary artery disease on contrary we found that majority of our patients had normal BMI. BMI had significant correlation with CRP in our study.

7.4 CRP

Majority of patients (89) 77.39% of diabetics with ACS had elevated CRP more than 3 mg/dl (Normal range in

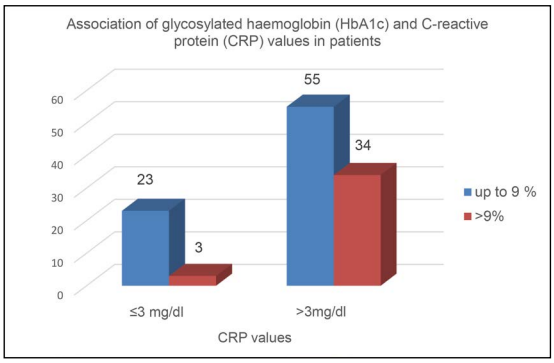

Figure 1. Association of Glycosylated Haemoglobin (Hba1c) and C-Reactive Protein (CRP) Values in Patients.

HbA1c Values	C-Reactive Protein (CRP) values						p Value
	≤3 mg/dl		>3 mg/dl		Total		
	N	%	N	%	N	%	
up to 9 %	23	20.00%	55	47.83%	78	67.83%	**0.01046< 0.05**
>9%	3	2.61%	34	29.57%	37	32.17%	
Total	26	22.61%	89	77.39%	115	100.00%	

our lab: 0 to 0.6 mg/dl). This explains the correlation of inflammatory marker that is CRP with perpetuating low grade inflammatory state of diabetes. This finding is also similar to correlation of CRP with coronary artery disease noted in study by Nyandak[6]

The CRP values in 9 (7.83%) patients were ≤1 mg/dl while 17 (14.78%) patients had CRP levels in the range of 1-3 mg/dl. The mean CRP value of patients was 4.24 ± 1.94 mg/dl.

7.5 HbA1c

70 (60.9%) and 22 (19.1%) patients had HbA1c values in the range of 7 - 9% and 9 - 10% respectively. 15 (13.1%) patients had HbA1c values in the range of >10%. The mean HbA1c value of patients was 8.31 ± 1.24%. So we found that in our study many patients had poor blood sugar control in span of last 3 months. Thus elevated HbA1c is a significant risk factor for cardiovascular disease was demonstrated in proved in our study. Similarly shown in a study Khaw[7] while 8 (6.9%) patients had HbA1c values in the range of ≤7%.

7.6 CRP and HbA1c

It was observed that significantly higher number of patients 78 (67.83%) with elevated CRP values had HbA1c values in the range of 6.5 to 9%. It was shown in our study that CRP was significantly correlated with HbA1c with Pearson correlation of p<0.05. This finding in our study strengthens the correlation of CRP and HbA1c as a risk of cardiovascular disease. This is in concordance with study of Sashidharan[8], Abdul razzak[9], Nyandak *et al.*,[6].

7.7 Blood Sugar

The mean FBS and PPBS values of patients were 168.27 ± 13.79 mg/dl and 242.87 ± 22.54 mg/dl respectively. As blood sugar were deranged in majority of patients in our study, explains the concept of link of hyperglycemia with endothelial vascular inflammation. It can also be concluded in our study that elevated fasting blood sugar having predilection for increased CRP level similarly demonstrated by Babu LE and Joshi[10].

7.8 Lipid Profile

The Mean±SD lipid profile parameters of patients in our study are summarized as follows: Cholesterol 186.27 ± 12.81 mg/dl, Triglyceride192.10 ± 41.77 mg/dl, VLDL 36.71 ± 2.97 mg/dl, LDL 124.32 ± 30.34 mg/dl and HDL 41.22 ± 5.66 mg/dl respectively. It was found in our study that CRP was significantly correlated with HDL having pearson correlation for both p<0.05**.** Deranged total cholesterol and triglyceride in majority of our patients indicated the link of dyslipidemia and diabetes. Both the condition aggravates the risk of cardiovascular disease.

7.9 ACS in DM and ACS in DM with HTN

In our study 37 patients of ACS were only diabetics and 78 patients with ACS were having diabetes and hypertension both. This clearly demonstrates the fact that as risk factor doubled incidence of coronary artery disease also increased to a significant proportion in our study.

8. Duration of Diabetes

Our study 66 patients were suffering from diabetes less than 5 years, 34 patients were diabetics for 5 to 10 years and 15 patients were diabetics for more than 10 years.

9. End Organ Damage

In our study 78 patients had retinopathy, 24 patients had retinopathy as well as nephropathy and 10 patients had only neuropathy, 3 patients did not have evidence of end organ damage.

10. Killip Classification

50 (43.5%) and 29 (25.2%) patients were in Killip Class I and Killip Class II respectively while 25 (21.7%) and 11 (9.6%) patients were in Killip class III and Killip class IV respectively. Thus in our study population, we found that majority of patients of acute coronary syndrome 50 (43.5%) belonged to low risk group that is Killip classification I. It was found in our study that Killip Classification was not significantly associated and C- Reactive Protein (CRP) as well as Glycosylated Haemoglobin (HbA1c) values in our patients as Pearson correlation was p>0.05.

11. Cardiac Biomarker

The Mean±SD cardiac biomarker parameters of patients are as follows: Troponin T 0.89 ± 0.29 ng/ml, CKMB 5.88 ± 0.46 ng/ml. This demonstrated the relationship of

elevated cardiac biomarker with acute coronary syndrome in our study.

12. Echo Cardiography

The Mean±SD echocardiography parameters of patient's LV Ejection Fraction (LVEF) was 58.89 ± 7.22%. It was also observed that only 15 patients (13.04%) had RWMA in our study.

13. ECG

In our study 82 patients had STEMI and 33 patients had NSTEMI.

14. Biochemical Parameters

The Mean±SD biochemical parameters of patients representing hepatic and renal indices were near normal range: SGOT 34.57 ± 17.97 and SGPT 33.82 ± 17.67, eGFR 105.03 ± 8.67.

15. Discussion

A hospital based descriptive study was conducted with 115 patients to evaluate correlation of C-Reactive Protein and Glycosylated Haemoglobin in patients of diabetes suffering from acute coronary syndrome.

Diabetes mellitus is commonly associated with both microvascular and macrovascular complications. Increasing evidence supports that atherosclerosis is a co-morbid condition in the diabetic patients. Impairment of vascular endothelial function is an initial step in the development of cardiovascular disease. There is important contribution of inflammation and oxidative stress to the pathogenesis of accelerated atherosclerosis in diabetes.

OxLDL when recognised by macrophages is converted into foam cells, which is a key event in atherogenesis. The central role of dyslipidemia in causing progression of atherosclerosis in adults with diabetes has been elucidated[4].

Recommendations for the diagnosis of diabetes are based on the relationship of fasting glucose and glycated hemoglobin with micro vascular disease. Studies suggest that glycated hemoglobin values in the normal range can identify persons at increased risk for coronary heart disease, stroke, and death before the diagnosis of diabetes, indicating that glycated hemoglobin is a useful marker of cardiovascular risk and death from any cause. The J-shaped relation between the glycated hemoglobin value and the risk of death from any cause suggests that further exploration of the health risks associated with the low-normal glycaemia state and possible nonglycemic determinants of glycated hemoglobinis warranted.

Increased CRP is an indicator for increased chances for cardiovascular disease. CRP levels are increased in patients with diabetes and also associated with HbA1c in people without diabetes[6]. However, literature is obscure about the correlation of glycaemia control in terms of HbA1C and levels of CRP. In the present study, majority of the patients were males with the mean age of 56.13 ± 12.10 year with mean BMI of 24.57 ± 3.10 kg/m^2. This was similar to the studies of Singh S[11], Pasupathi P[12] and Sasidharan A[8].

It was found that in our study the mean CRP value of patients was 4.24 ± 1.94 mg/dl, also mean HbA1c value of patients which was on higher side that is 8.31 ± 1.24% suggested their correlation in patients of diabetics with acute coronary syndrome. This is comparable to the studies of Singh S[11] and Abdul Razzaq[9]. It was observed in the present study that significantly higher number of patients with elevated CRP values had HbA1c values in the range of 6.5-9%. There was significant association of Glycosylated Haemoglobin (HbA1c) and C-Reactive Protein (CRP) values in patients as per Chi-Square test ($p<0.05$). This is in concordance to the studies of Sasidharan[8], Abdul Razzaq[9] and Nyandak[6].

Sasidharan[8] population based study assessing a correlation between glycemic control and C-Reactive Protein (CRP) in patients with T2DM and to assess if good control of glycosylated hemoglobin (HbA1c) decreases the CRP values reported CRP was directly related with cardiovascular diseases in patients suffering from T2DM. PPBS, HbA1c and Triglyceride showed highly significant correlation with CRP. Other risk factors such as waist–hip ratio, body weight, BMI, LDL cholesterol and serum creatinine also had positive correlation but were of lesser significance, whereas HDL showed a negative correlation. According to Pearson correlation, values obtained <0.05 which was highly significant, for total cholesterol was 0.53 with $P<0.05$, which was again highly significant and for triglyceride was 0.37 with $P<0.05$ which was also highly significant.

Abdul Razzaq[9] cross-sectional observational study determining the association between (admission glucose and HbA1c) and short term outcome in patients not known to be diabetics presented with ACS reported there was an association between BMI, hyperlipidemia, hypertension and smoking with elevated HbA1C but without statistically significant difference.

In our study, CRP was significantly correlated with HbA1c with Pearson correlation ($p<0.05$). Similar observations were noted in the studies of Singh S[11], Mani VE[13], Nyandak T[6], Selvin E[14], Khaw KT[7], Malmberg K[15], Basar[16] and Babu and Joshi[10].

Selvin E[14] and Khaw KT[7] showed that an elevated HbA1c is associated with increased cardiovascular risk in patients with and without diabetes. The coronary heart disease risk score given by Framingham, Michelle and others stated that the CRP levels were significantly related to 10-year Framingham coronary heart disease risk categories. King DE[17] study reported a strong correlation between HbA1c levels and CRP. Besides, they also found that CRP levels were associated with HbA1c levels.

The Mean±SD lipid profile parameters of patients in our study are summarized as follows: Cholesterol 186.27 ± 12.81 mg/dl, Triglyceride 192.10 ± 41.77 mg/dl, VLDL 36.71 ± 2.97 mg/dl, LDL 124.32 ± 30.34 mg/dl and HDL 41.22 ± 5.66 mg/dl respectively. This is consistent with the study of Abdul Razzaq[9]. Dyslipidemia has been proven as one of the major risk factor for CHD. Both triglyceride and LDL-cholesterol are associated with atherogenic process and there is increasing evidence that HDL-cholesterol prevents atherogenesis. Pasupathi[12] population based study examining the combinational effect of cardiac and biochemical markers in diabetic patients with cardiovascular disease observed fasting plasma glucose level and Glycosylated Haemoglobin (HbA1c), total cholesterol, triglycerides, VLDL, LDL-C, Cardiac troponins levels were elevated in cardiac patients with and without diabetes, HDL level was lower in cardiac patients with diabetes as compared to the control subjects.

The Mean±SD biochemical parameter of patients is summarized as SGOT 34.57 ± 17.97 and SGPT 33.82 ± 17.67, eGFR 105.03 ± 8.67 respectively. The Mean±SD cardiac biomarker parameters of patients are summarized as follows: Troponin T 0.89 ± 0.29 ng/ml, CKMB 5.88 ± 0.46 respectively. This is concordant to the studies of Singh[11] and Pasupathi[12]. The Mean±SD echocardiography parameters of patients in our study LV ejection fraction (%) was 58.89 ± 3.05. These findings were consistent with the studies of Singh[11] and Abdul Razzaq[9].

It was observed in our study that 50 (43.5%) and 29 (25.2%) patients were in Killip Class I and Killip Class II respectively while 25 (21.7%) and 11 (9.6%) patients were in Killip class III and Killip class IV respectively. The mean FBS and PPBS values of patients were 168.27 ± 13.97 mg/dl and 242.87 ± 22.54 mg/dl respectively. It was observed in our study that a significantly higher number of patients with elevated CRP values belonged to Killip Class I. But It was found in our study that Killip Classification was not significantly associated and C-Reactive Protein (CRP) as well as Glycosylated Haemoglobin (HbA1c) values in our patients as Pearson correlation was $p>0.05$.

16. Conclusion

As diabetes is a perpetual state of low grade vascular endothelial inflammation and C- Reactive Protein is inflammatory marker. In our study C-Reactive Protein had correlation with Glycoselated Haemoglobin, Age, Body Mass Index.

We conclude that deranged C-Reactive Protein, Glycoselated Haemoglobin, lipid profile are significant risk factor for coronary artery disease. As Atherosclerosis also exhibits a feature of inflammation we conclude that C Reactive Protein can be considered a marker of deranged lipid profile and atherosclerosis.

Hence, we conclude that elevated C-Reactive Protein and Glycosylated Haemoglobin are better correlated as poor prognostic marker for cardiovascular event in patients of diabetes suffering from acute coronary syndrome.

Here we recommend measures should be taken to follow proper diet, exercise, pharmacological therapy for deranged lipid profile. As increased body mass index and deranged lipid profile are risk for cardiovascular disease in both diabetes and non diabeteics population.

17. Limitations and Comparison with our Study

Due to cost factor High Sensitive C Reactive Protein (HSCRP) was not done in our study. High sensitive CRP levels are better correlated severity of coronary artery disease as documented in study by Nyandak[6].

As it was descriptive observational study, we were restricted to aims and objective, detail evaluation of HbA1c and C Reactive Protein and their correlation with LV systolic and diastolic function was not done. Further study will be required as demonstrated in a study by Abdul razzak[9] that HbA1c on admission is a powerful predictor of LV systolic diastolic function as a major adverse event of acute coronary syndrome in patients not known to be diabetics.

Similarly due to above reason detail evaluation of cardiac biomarker and biochemical markers detail correlation of end organ damage were not done. Further large scale studies will be required to study correlation of BNP, NT-pro-BNP for symptomatic and asymptomatic left ventricular dysfunction in patients of diabetes as it was shown in a study by Pasupathi[12].

Similarly due to above reason detail evaluation of cardiac biomarker and biochemical markers were not done. Further large scale studies will be required to study correlation of BNP, NT-pro-BNP for symptomatic and asymptomatic left ventricular dysfunction in patients of diabetes. This was shown in a study by Pasupathi *et al.*

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