Original Article

Correlation between Inflammatory Marker and Glycemic Control in Patients with Ischemic Heart Disease

Mohsin Ahmed[1], Md Mesbahul Islam[2] , Mohammad Arifur Rahman[3], Khandaker Abu Rubaiyat[4] , C. M Khudrate-E-Khuda[5], Kazi Abul Fazal Ferdous[6] , Bikash Chandra Das[7], Sanoat Kalam Linda [8]

Abstract:

Background: Recent evidence suggests that inflammatory markers and poor glycemic control are significantly associated with the development of cardiovascular complications. The purpose of this study was to determine the association between inflammatory marker (CRP) and glycemic status (HbA1c) in ischemic heart disease patients.

Method: This cross sectional study was performed on 668 patients of ischemic heart disease in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, who underwent Coronary angiogram from January 2017 to December 2017. CRP value were divided into normal (<6 mg/L), borderline (6-10 mg/L) and high (>10 mg/L) and HbA1c was divided <6.5% and ≥6.5%. After performed Coronary angiography the extent of disease was divided into insignificant CAD of (<50% stenosis), significant CAD considered as >50% stenosis and single vessel, double vessel, triple vessel CAD and normal coronaries. The relationship between CRP with HbA1c was analyzed by Chi square test. ANOVA test was used to analyze the continuous variables, shown with mean and standard deviation. Pearson's correlation coefficient was used to test the relationship between CRP and HbA1c in CAD patients. p value <0.05 was considered as statistically significant.

Result: Most (65.0%) of the patients belonged to age 41-60 years. The mean age was found 51.4±10.7 years. Majority (82.3%) of patients were male. Among risk factors, highest (40.0%) patients had hypertension followed by 209 (31.3%) diabetes mellitus and 204 (30.5%) smoker. Positive correlation was found (r=0.220, p= 0.001) between HbA1c with CRP in CAD patients. High CRP was found 138(38.4%) in <6.5% HbA1c and 187(60.5%) in ≥6.5 percent HbA1c. The difference was statistically significant (p<0.05). Multi variable logistic regression was found high HbA1c, high CRP and diabetes mellitus were statistically significant (p<0.05) in severe CAD (Double and triple vessel) patient.

Conclusion: Positive correlation was found between serum levels of CRP and HbA1c in CAD patients. Thus, aiming at good glycemic control and estimation of serum CRP levels will possibly be of help in planning early intervention, thereby preventing further complications which in turn may help preserve cardiac functions in ischemic heart disease patients.

Keywords: Coronary artery disease, C-reactive protein, HbA1c

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1. Associate Professor, Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh
2. Registrar, Department of Cardiology, Ibn Sina Hospital, Dhaka, Bangladesh
3. Junior Consultant, Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh
4. MD, Final Part, Department of Cardiology , Dhaka Medical College, Dhaka, Bangladesh
5. Junior Consultant, Department of Cardiology, Dhaka Medical College, Dhaka, Bangladesh
6. Medical Officer, Department of Cardiology , Dhaka Medical College, Dhaka, Bangladesh
7. Registrar, Department of Cardiology, Dhaka Medical College, Dhaka, Bangladesh
8. FCPS Part-II, Department of Medicine, Bangabandhu Sheikh Mujib Medical Unerversity, Dhaka, Bangladesh

Address of Correspondence: Dr. Mohsin Ahmed, Associate Professor, Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh. Cell: +8801613393186, E-mail: mohsinsohel07@gmail.com

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Introduction:

The autoimmune response associated with overproduction of T helper-1 (Th1) cytokines which activate macrophage production of proinflammatory mediators interleukin-6 (IL-6) and TNF-±.[1] IL-6 is produced also by a variety of cells such as adipocytes, which produce 30% of the circulating IL-6, fibroblasts and endothelial cells.[2] It mediates damage to micro- and macro-vascular tissues, altered insulin secretion either directly or through stimulation of free fatty acid production and altered glucose homeostasis.[3] C-reactive protein is an acute-phase protein and a marker of non-specific inflammation synthesized in the liver. The biosynthesis of CRP is largely regulated by IL-6.[4] Plasma markers of inflammation, such as CRP and IL-6 are positively associated with risk of vascular disease in non diabetic individuals.[5] Recently, inflammation has been considered, at least in part, to lead to the development and progression of atherosclerosis.[6]

C-reactive protein (CRP), a marker of systemic inflammation, is emerging as an independent risk factor for cardiovascular disease.[7–9] High CRP levels have been linked to an increased risk of thrombotic events including myocardial infarction.[9–11] Elevated CRP levels have also been linked to an increased risk of later development of diabetes.[12,13] Furthermore, CRP levels are higher in people with diabetes compared with those without diabetes.[14–16] Less is known about whether CRP in people with diabetes is related to level of glycemic control. Wu et al.[17] found that CRP is associated with HbA1c levels.

Elevated glycohemoglobin A1 (HbA1c) is an established predictor for developing atherosclerosis.[18,19] Eeg-Olofsson et al.[20] studied a total of 7,454 patients from the Swedish National Diabetes Register over a period of 5 years (aged 20–65 years, diabetes duration 1-35 years) and found a progressively increasing risk of coronary heart disease and cardiovascular diseases with higher HbA1c levels independent of traditional risk factors. HbA1c is a better marker for determining risks of CAD and mortality than fasting blood glucose and even non-diabetic patients with elevated HbA1c levels are also at increased risk for CVD and mortality.[21] Both enhanced inflammation and hyperglycemia contribute to the development and progression of atherosclerosis and are frequently found in patients with clinically advanced disease. Given the interrelation between inflammation, hyperglycemia, and atherosclerotic disease.

There was a statistically significant positive correlation of serum hsCRP levels with HbA1c indicating the role of poor glycemic control. Studies have shown similar association between hyperglycemia and inflammation.[22] It is known that glycation triggers the inflammatory process, leading to a rise in hsCRP levels. Thus, hsCRP can predict the onset of glycation-induced inflammatory process secondary to poor glycemic control.[23]

To provide further insight into the role of inflammation in the development of cardiovascular disease, we sought to elucidate the link between level of glycemic control and inflammation. The purpose of the study was to investigate the correlation between CRP and HbA1c in the patients with ischemic heart disease.

Methodology:

This cross sectional study was performed on 668 patients of ischemic heart disease (CSA, UA, NSTEMI and STEMI) in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, who were underwent Coronary angiography from January 2017 to December 2017. Demographic variables, such as age and sex, west and hip circumference and angiography results were recorded. After explaining the aims of the study and obtaining the patient's approval for participation blood samples were sent. CRP value were divided into normal (<6 mg/L), borderline (6-10 mg/L) and high (>10 mg/L)[19] and HbA1c was divided <6.5% and e"6.5%. After performed Coronary angiography the extent of disease was divided into insignificant CAD of (<50% stenosis), significant CAD considered as >50% stenosis[20] and single vessel, double vessel, triple vessel CAD and normal coronaries. The relationship between CRP with HbA1c was recorded by Chi square test. Statistical Package for the Social Sciences (SPSS) version 23.0 for windows was used to analyze the data. Categorical variables were expressed as proportions (percentages) and numerical data was expressed as means (standard deviations) and ranges. ANOVA test was used to analyze the continuous variables, shown with mean and standard deviation. Pearson's correlation coefficient was used to test the relationship between CRP and HbA1c in CAD patients. p value <0.05 was considered as statistically significant.

Results:

This cross sectional study was performed on 668 patients of ischemic heart disease (CSA, UA, NSTEMI and STEMI) in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, who were underwent Coronary angiography from January 2017 to December 2017.

Most (65.0%) of the patients belonged to age 41-60 years. The mean age was found 51.4±10.7 years with range from 25-85 years. Majority (82.3%) patients were male and 390 (58.4%) patients were illiterate (Table-1). In risk factors, highest 267 (40.0%) patients had hypertension followed by 209 (31.3%) diabetes mellitus, 204 (30.5%) smoker, 189

(28.3%) H/O ischemic heart disease and 151 (22.6%) dyslipidemia (Table-2). Positive correlation (r=0.220, p= 0.001) of HbA1c with CRP (Figure 1). High CRP was found 138(38.4%) in <6.5 percent HbA1c and 187(60.5%) in e"6.5 percent HbA1c. The difference was statistically significant (p<0.05) (Table III). Multi variable logistic regression was found high HbA1c, high CRP and diabetes mellitus were statistically significant (p<0.05) in severe CAD (Double and triple vessel) patients (Table IV).

Table-I

Demographic characteristics of the study subjects (n=668)

Demographic characteristics	Frequency	Percentage
Age (in years)		
≤40	123	18.4
41-60	434	65.0
>60	111	16.6
Mean±SDRange (min-max)	51.4±10.7(25–85)	
Sex		
Male	550	82.3
Female	118	17.7
Educational status		
Illiterate	390	58.4
Primary	110	16.5
Secondary	111	16.6
Higher	37	5.5
Graduate and above	20	3.0

Table-II

Distribution of the study subjects by clinical risk factors (n=668)

Risk factors	Frequency	Percentage
Diabetes mellitus	209	31.3
Hypertension	267	40.0
Dyslipidemia	151	22.6
Obesity	28	4.2
Smoking	204	30.5
Tobacco	97	14.5
Alcohol	2	0.3
Family history of CAD	31	4.6
H/O ischemic heart disease	189	28.3
Previous PTCA	11	1.6
Previous CABG	10	1.5

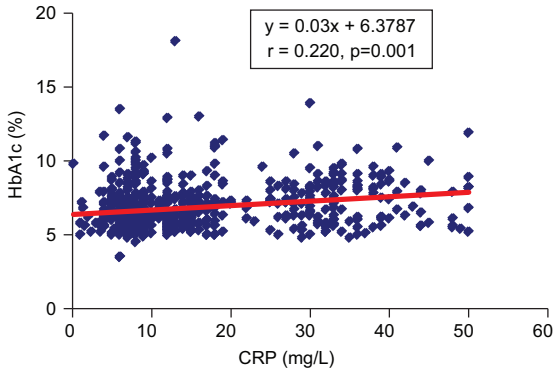

Fig.-1: *Scatter diagram showing the positive correlation (r=0.220, p= 0.001) of HbA1c with CRP (n=668).*

Table III

Association between HbA1c with CRP of the study population

CRP	HbA1c		p value
	<6.5n (%)	≥6.5n (%)	
Normal (<6 mg/L)	33 (9.2)	23 (7.4)	0.001[s]
Borderline (6-10 mg/L)	188 (52.4)	99 (32.0)	
High (>10 mg/L)	138 (38.4)	187 (60.5)	

Data were analyzed by Chi-square test, s= significant

Table-IV

Multi variable logistic regression analysis for severe CAD

	Adjusted OR	95% CI		P Value
		Lower	Upper	
HbA1c (e"6.5)	0.261	0.025	0.882	0.023[s]
CRP (>10 mg/L)	30.222	8.874	99.389	0.001[s]
Diabetes mellitus	0.103	0.011	0.953	0.045[s]
Hypertension	1.059	0.268	4.181	0.935[ns]
Dyslipidemia	0.698	0.146	3.346	0.653[ns]
Smoking	0.547	0.143	2.092	0.378[ns]
Constant	0.007	-	-	0.001[s]

s= significant, ns= not significant

DISCUSSION:

Recently, inflammation has been implicated in the development and progression of atherosclerosis. From the pathological viewpoint, all stages i.e. initiation, growth and complications of the atherosclerotic plaque, may be considered as inflammatory responses to vascular endothelial injury. Being the major cause of mortality and morbidity in patients with T1DM[24] it is very important to study and monitor markers of inflammation to define patients at higher risk of vascular complications.

Glycemic control, BMI, LDL cholesterol, HDL cholesterol, triglycerides, and systolic blood pressure were defined as the determinants of inflammatory activity in type 1 diabetes.[25,26]

In this present study it was observed that most (65.0%) of the patients belonged to age 41-60 years. The mean age was found 51.4±10.7 years with range from 25-85 years. Majority (82.3%) patients were male and 390 (58.4%) patients were illiterate. Similar report Muhammad et al.[27] found mean age of the study population was 51.5±9.5 years and most (65.7%) of the patient were male.

In this study, among the risk factors, highest 267 (40.0%) patients had hypertension followed by 209 (31.3%) diabetes mellitus, 204 (30.5%) smoker, 189 (28.3%) H/O ischemic heart disease and 151 (22.6%) dyslipidemia. This findings were also consistent with others studies like Razban et al.[28]; Muhammad et al.[27] and Seyedian et al.[29].

From this study, we cannot infer, whether poor glycemic control leads to inflammation or whether inflammation leads to higher glucose levels (or whether a third factor influences both). Prospective studies are needed to evaluate that question. However, either direction of causality would have important implications. If poor glycemic control leads to inflammation, then better glycemic control should lower inflammation and therefore lower the risk of cardiovascular complications.

In this study positive correlation was found (r=0.220, p= 0.001) between HbA1c with CRP in CAD patients. Fawaz et al.[30] found their study a positive correlation of inflammatory marker (CRP) and HbA1c which supports other studies.[2,31] This can be explained by the fact that HbA1c reflects the biological activities of hyperglycemia and advanced glycation end products, all of which can induce inflammation.[32] Hyperglycaemia has an indirect influence on atherosclerosis through lipid changes. It increases potentially atherogenic forms of small VLDL and small dense LDL which are susceptible to glycation and oxidation. However, chronic hyperglycaemia may be a separate risk factor for accelerated macroangiopathy.[33] Roopakala et al.[34] reported that positive correlation (r=0.347, p= 0.008) of HbA1c with CRP in diabetic nephropathy.

Positive correlation coefficient between hemoglobin A1c and CRP levels in studied patients (r = 0.371, p=0.05).[35] Study done by Tutuncu et al.[36] on comparison of hs- CRP levels in new Diabetes groups observed a positive correlation between hs-CRP levels and age, BMI, waist, hip, SBP, DBP, pulse, FPG, HbA1c, TG, non-HDL cholesterol; and there was a negative correlation with HDL-cholesterol and eGFR. Wu et al.[17] reported that high levels of hs-CRP were correlated with high levels of HbA1c and FPG in men and with only FPG in women.

In this study, high CRP was found higher (60.5%) at ≥6.5 percent HbA1c level. The difference was statistically significant (p<0.05). King et al.[37] reported that elevated HbA(1c) levels (e”9.0%) had a significantly higher percent of elevated CRP than people with low (<7%) HbA(1c) levels (P <0.001).

Festa et al.[38] found links between CRP and insulin resistance. Other studies have related hyperglycemia to inflammation by demonstrating simultaneous inflammation, endothelial dysfunction, and insulin resistance at the physiologic level.[39,40] One of the several mechanisms proposed is oxidative stress on the endothelium, which promotes inflammation and is enhanced by hyperglycemia.[41-43] The current study demonstrates that higher HbA1c is significantly associated with elevation of CRP. These results imply a significant relation between inflammation and glycemic control in people with established CAD.

Multi variable logistic regression was found high HbA1c had 0.261(95% CI 0.025 to 0.882), high CRP had 30.222 (95% CI 8.847 to 99.389) and diabetes mellitus had 0.103 (95% CI 0.011 to 0.953) times increase in odds having severe CAD (Double and triple vessel). Which were statistically significant (p<0.05).

Therefore, detection of inflammatory marker and close observation of their glycemic control is essential to prevent cardiovascular complications. Early and effective prevention of cardiovascular disease will improve lifestyle with the emphasis on disease prevention.

Conclusion:

There is a positive correlation between serum levels of CRP and HbA1c in CAD patients. Thus, aiming at good glycemic control and estimation of serum CRP levels will possibly be of help in planning early intervention, thereby preventing further complications which in turn may help preserve cardiac functions in ischemic heart disease patients.

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