C-REACTIVE PROTEIN IN PATIENTS WITH ACUTE CORONARY SYNDROME: ASSOCIATION WITH CORONARY MARKERS, LIPID PROFILE AND MARKERS OF COAGULATION

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ABSTRACT

Objectives: To determine levels of C-reactive protein (CRP) and its association with coronary markers, lipid profile and markers of coagulation in patients of acute coronary syndrome (ACS).

Study Design: Case control study

Place and Duration of study: The study was conducted at Shifa college of Medicine and Shifa international hospital for a period of one year (November 2005-December 2006).

Patients and Methods: Sixty nine age matched controls and 133 consecutive patients of ACS were included in the study. CRP were measured by immunoturbidometric method, MB fraction of creatine kinase (CK-MB) and Troponin-I by micro-particle enzyme immunoassay, lipid levels by Colorimetric Enzymatic methods, platelets by celldyn and coagulation markers were measured by CA-50 Sysmax.

Results: At admission mean CRP levels, cardiac biomarkers, lipid profile and coagulation markers were significantly increased in patients of ACS versus controls. Within the patients of ACS the mean levels of CRP, CK-MB, Trop I, prothrombin time (PT) and activated partial thromboplastin time (APTT) were significantly raised in patients with ST-elevation myocardial infarction (STEMI) and non STEMI (NSTEMI) versus patients of unstable angina (UA). Association between CRP levels and coronary markers, coagulation markers and lipid profile was found to be non significant.

Conclusion: The CRP levels were increased in patients with ACS as compared to controls. The CRP levels were insignificantly correlated with coronary markers (CK-MB, Trop I), coagulation markers (platelet count, PT, APTT), and lipid profile (cholesterol, triglyceride, HDL and LDL cholesterol) in patients with ACS.

Keyword: C-Reactive Proteins, Lipid Profile, Acute Coronary Syndrome Coagulative Markers

INTRODUCTION

Coronary heart disease (CHD) is the single most common cause of death in the developed World and its incidence is increasing in the developing countries[1]. A number of predisposing factors affect the development of ischemic heart disease (IHD) and to date more than 246 risk factors have been identified including dyslipidemia, a major risk factor for development of atherosclerosis (AS)[2,3]. Among other major risk factors hypertension, diabetes mellitus, family history of IHD, infections and cigarette smoking are also associated with increased risk of AS and coronary artery disease (CAD)[4]. In patients with CHD, risk stratification is important as information about probability of cardiovascular events in future can help target therapy and resources to those most likely to benefit[5]. With growing evidence that AS is an inflammatory process initiated by vascular injury, oxidized LDL, reactive oxygen species, diabetes mellitus and infections, several plasma markers of inflammation have been evaluated as potential tools for the prediction of the coronary events[6,7]. These markers of inflammation include among others serum amyloid A, IL-6, fibrinogen, homocystein, apolipoprotein-A, apolipoprotein B-100 and C-reactive protein (CRP)[8].

CRP is an acute phase reactant protein produced in the liver in response to injury, inflammation and acute infections. CRP reflects the presence and intensity of inflammation and is now regarded as a surrogate marker and mediator of the atherothrombotic diseases[9]. In a study comparing the magnitude of predictive value to twelve other putative risk factors, CRP was found to be more predictable risk marker

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Received: 13 Dec 2008; Accepted: 02 April 2009

for ACS and stroke than others[10]. Elevation in the serum CRP levels seems to correlate with the prognosis, irrespective of the extent of myocardial damage[11] and may reflect an important role of a pre-existing inflammation[12] or a higher prevalence of myocardial necrosis[13] and ischemic reperfusion damage[14].

A number of studies have reported that CRP levels increase during acute myocardial infarction (AMI) and unstable angina (UA)[15,16]. The present study was designed to evaluate the CRP levels in patients with ACS (STEMI, NSTEMI, and UA) and its correlation with lipid profile and markers of coagulation.

MATERIALS AND METHODS

The case control study was carried out at the Shifa College of Medicine and Shifa International Hospital Islamabad from November 2005 to December 2006. A total of 202 subjects, 69 controls and 133 patients of ACS were recruited in this study. All patients were evaluated by taking detailed history and physical examination. The variables included in the study were age, sex, CK-MB, Trop I, CRP, cholesterol, triglyceride, HDL, LDL cholesterol, and coagulation markers; platelet count, PT and APTT.

The inclusion criteria for the patients of ACS were those of American College of Cardiology and European Society of Cardiology[17].

The criteria for STEMI/ NSTEMI is as follows

1. Typical Chest pain
2. ECG alterations:

New or presumed new ECG alterations: ST segment elevation at J point in two or more contiguous leads; and for non ST segment elevation, ST segment depression or T wave abnormalities in two or more contiguous leads.

3. Biochemical Changes

- Maximum concentration of CK-MB exceeding the 99th percentile of the values for a reference control group on two successive samples.
- Maximum concentration of troponin I exceeding the 99th percentile of the values for a reference control group on at least one occasion during the first 24 hour after the indexed clinical event.

4. New or presumed new echocardiographic alterations: cardiac wall motion abnormalities.

Criteria for UA

1. Typical chest pain and ECG modifications, such as ST depression or T wave inversion in ≥ 2 leads.
2. Absence of biochemical alterations
3. Absence of new or presumed new echocardiographic alterations: cardiac wall motion abnormalities.

Patients with history of infection or inflammation during the last 15 days, or with hepatic and renal disease, hyperlipidemia and those who did not sign the informed consent proforma were excluded from the study.

On these criteria, 37 patients were diagnosed as patient of STEMI, 38 of NSTEMI, and 58 as patients of UA.

Venous blood drawn at time of admission was analyzed for CK-MB, Trop I, CRP, coagulation markers (platelet count, PT, APTT) and lipid components; (cholesterol, triglyceride, HDL, LDL cholesterol).

The plasmatic CRP levels were estimated with particle enhanced immunoturbidimetric method using Hitachi 911 from Roche Diagnostic Germany. The CK-MB and Trop I were determined by Microparticle Enzyme immuno-assay (MEIA) using AxSYM system from Abbott Laboratories USA. The platelet count was done using Celldyn from Abbott Laboratories USA, while PT and APTT were done by CA-500 Sysmax from Japan. Total cholesterol, TG, HDL and LDL cholesterol plasmatic concentrations were measured with Colorimetric Enzymatic methods using Hitachi 911 from Abbott Laboratories USA.

STATISTICAL ANALYSIS

Data had been analyzed using SPSS version 15. Descriptive statistics were used to describe the data. Categorical variables were analyzed by chi-square test and the continuous variables with't' test. Correlation between continuous variable was determined by Pearson's correlation test. P value <0.05 was considered to be statistically significant.

RESULTS

Comparison of clinical characteristics and various traditional risk factors of CAD in patients with ACS and controls is shown in Table 1. The patients of ACS had a statistically high significant difference in the percentage of diabetes mellitus, blood pressure, smoking, triglyceride levels, family history of IHD and hypertension as compared to controls. A statistically high significant difference was also seen in patients of UA, NSTEMI and STEMI versus controls in the percentage of DM, systolic blood pressure, diastolic blood pressure, smoking and triglyceride, while the percentage of family history of hypertension and family history of IHD was significantly increased in the patients of NSTEMI and STEMI versus controls (Table-1).

At the time of admission a statistically high significant difference was seen in patients of ACS as compared to controls when acute phase protein-CRP, cardiac biomarkers CK-MB, Trop I, components of lipid profile (cholesterol, TG, LDL) and coagulation markers; platelet count and PT were measured (Table-2). Within the patients of ACS, the mean baseline plasma levels of CRP, CK-MB, Trop I, and cholesterol, TG, LDL and PT were highly significant in patients of STEMI and NSTEMI versus controls. Similarly, a highly significant difference was also noted in the levels of APTT and platelet count in patients with STEMI versus controls (Table-2).

When the coronary markers, coagulation markers; PT and APTT and acute phase protein, CRP were measured, a highly significant difference was seen in patients of NSTEMI and STEMI versus UA. Where as, the levels of the parameters mentioned above between patients of STEMI and NSTEMI were non significant except trop I (Table-3).

A positive correlation was seen between baseline Trop I and CK-MB levels in patients with UA ($r = 0.342$, $p = 0.009$), NSTEMI patients ($r = 0.908$, $p = 0.000$) and STEMI patients ($r=0.714$, $p=0.000$). However, in patients of ACS, the correlation between CRP levels and coronary markers CK-MB ($r = -0.42$, $p = 0.631$), Trop I ($r = 0.111$, $p = 0.202$), platelet count ($r = 0.127$, $p = 0.146$), PT ($r = 0.126$, $p = 0.148$), APTT ($r = 0.156$, $p = 0.073$), and with cholesterol ($r = -0.084$, $p = 0.335$), triglyceride ($r = -0.085$, $p = 0.329$), HDL ($r = -0.038$, $p = 0.663$), and LDL cholesterol ($r = -0.44$, $p = 0.613$)) were found to be non significant.

In patients with unstable angina, the correlation between CRP levels and coronary markers CK-MB ($r = -0.124$, $p = 0.354$), Trop I ($r = -0.007$, $p = 0.960$), coagulation makers platelet count ($r = -0.020$, $p = 0.882$), PT ($r = 0.095$, $p = 0.479$), APTT ($r = -0.009$, $p = 0.944$) and with lipid profile cholesterol ($r = 0.068$, $p = 0.613$), triglyceride ($r = -0.239$, $p = 0.071$), HDL ($r = 0.053$, $p = 0.692$), and LDL cholesterol ($r = 0.071$, $p = 0.598$)) were also non significant.

In Non-STEMI patients the CRP levels did not show statistically significant correlation with CK-MB ($r = -0.094$, $p = 0.573$) Trop I ($r = 0.072$, $p = 0.666$)), coagulation makers platelet count ($r = 0.103$, $p = 0.538$), PT ($r = -0.033$, $p = 0.842$), APTT ($r = 0.064$, $p = 0.702$), and cholesterol ($r = -0.178$, $p = 0.286$), triglyceride ($r = 0.018$, $p = 0.917$), HDL ($r = -0.222$, $p = 0.180$), and LDL cholesterol ($r = -0.133$, $p = 0.426$).

A non significant correlation was also seen in patients of STEMI when CRP levels were correlated with CK-MB ($r = -0.297$, $p = 0.075$), Trop I ($r = -0.197$, $p = 0.242$), platelet count ($r = 0.157$, $p = 0.353$), PT ($r = 0.027$, $p = 0.872$), APTT ($r = 0.171$ $p = 0.311$), and lipid profile cholesterol ($r = -0.178$, $p = 0.291$), triglyceride ($r = -0.185$, $p = 0.274$), HDL ($r = 0.137$, $p = 0.417$), and LDL cholesterol ($r = -0.099$, $p = 0.560$).

DISCUSSION

The present study illustrates that the plasma CRP levels were significantly increased in patients of ACS, NSTEMI and STEMI at time of admission as compared to controls. These results are in consistent with Tomado et al[18] and Gavusoglu et al[19] who demonstrated increased CRP levels in patients with ACS as compared to the controls. A positive correlation was present between CRP levels and culprit coronary lesion and worse clinical outcome in these patients than in patients who had normal CRP levels. The inflammatory process could be one of the mechanisms causing plaque rupture that leads to increased CRP levels in patients with ACS[20].

Table-1: Comparison of clinical characteristics and coronary risk factors in patients with acute coronary syndrome, unstable angina, non STEMI, STEMI and controls

	Controls Patients	ACS Patients	UA Patients	NSTEMI Patients	STEMI
Age ≥ 60 years	50.7	55.6	69.0	39.5	51.4
Sex Male	66.7	63.2	53.4	65.8	75.7
DM	29.0	62.4	56.9	55.3	78.4
Section HTN	2.9	28.6	25.9	31.6	29.7
Diastolic HTN	4.3	24.1	27.6	23.7	18.9
Smokers	15.9	55.6	56.9	44.7	64.9
Hypercholesterolemia	33.3	45.1	43.1	50.0	43.2
Hypertriglyceridemia	14.5	66.2	72.4	65.8	56.8
Family H/O IHD	18.8	33.1	17.2	39.5	51.4
Family H/O hypertension	24.6	9.0	8.6	7.9	10.8
Family H/O diabetes	18.8	19.5	17.2	26.3	16.2

ACS: acute coronary syndrome; UA: unstable angina; NSTEMI: non ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction; DM: diabetes mellitus; HTN: hypertension; H/O: history of; IHD: ischemic heart disease; Values are expressed in percentage; *, p = <0.05 vs controls; (p <0.05 is statistically significant).

Table-2: Comparison of age, biochemical and haematological parameters of patients with acute coronary syndrome, unstable angina, non ST segment elevation myocardial infarction and ST segment elevation myocardial infarction versus controls

	Controls Patients	ACS Patients	UA Patients	NSTEMI Patients	STEMI
Age (Years)	59.67 ± 1.72	60.92 ± 1.04	62.40 ± 1.38	59.37 ± 2.00	60.19 ± 2.25
CRP (mg/L)	3.24 ± 0.33	11.35 ± 2.17 *	3.32 ± 0.33	16.17 ± 5.45 *	18.98 ± 5.05 *
CK-MB (ng/dl)	2.57 ± 0.23	39.62 ± 6.70 *	3.02 ± 0.29	54.61 ± 14.65 *	81.59 ± 15.88 *
Trop I (mg/dl)	0.092 ± 0.03	4.25 ± 0.62 *	0.06 ± 0.02	5.10 ± 1.26 *	9.96 ± 1.32 *
Cholesterol (mg/dl)	173.74 ± 4.72	190.94 ± 3.81*	184.12 ± 5.89	200.50 ± 7.83*	191.81 ± 6.00 *
TG (mg/dl)	132.39 ± 4.29	198.54 ± 11.09*	196.17 ± 12.52*	179.68 ± 14.71*	221.62 ± 31.30*
LDL (mg/dl)	99.32 ± 3.37	113.11 ± 3.32 *	106.74 ± 4.89	122.16 ± 6.96 *	113.78 ± 5.54 *
HDL (mg/dl)	40.10 ± 1.21	39.95 ± 0.87	38.84 ± 1.26	40.95 ± 2.02	40.68 ± 1.28
Platelet count (/cmm)	$2.47x10^5$ ± 9067	$2.79x10^5$*±8507	$2.64x10^5$ ± 12039	$3.03x10^5$ ± 17453	$2.78x\ 10^5$ 15703
PT (sec)	13.92 ± 0.15	16.45 ± 0.39 *	14.02 ± 0.32	18.91 ± 0.87 *	17.75 ± 0.68 *
APTT (sec)	30.73 ± 0.67	32.26 ± 0.52	30.64 ± 0.49	33.31 ± 1.34	33.72 ± 0.98 *

ACS: acute coronary syndrome; UA: unstable angina; NSTEMI: non ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction; CRP: C-reactive protein; CK-MB; MB iso-enzyme of creatine kinase; Trop-I: troponin I; TG: triglyceride; LDL: low density lipo-protein cholesterol; HDL: high density lipo-protein cholesterol; PT: prothrombin time; APTT: activated partial thrmboplastin time; Values are expressed as Mean ± SEM; *, p = <0.05 vs controls; (p <0.05 is statistically significant).

The low grade inflammation detected by CRP is most likely an indirect marker of increased cytokine response to inflammatory stimuli critical for atherosclerotic plaque vulnerability and plaque rupture[21]. These findings suggest that increased risk of future coronary events observed in patients with elevated serum CRP may be directly related to increased number of vulnerable plaques prone to rupture, which strengthens the role of CRP as a risk factor during development of CVD[22].

Auer J[23] and his colleagues had shown that the CRP levels increase 6-12 hours after the onset of symptoms in patients with ACS. It was suggested that the affected coronary vessels are small and the total number of activated macrophages are too small to be detected by increased CRP concentration.

Table-3: Comparison of biochemical and haematological characteristics of patients of unstable angina, non STEMI and STEMI.

	UA patients	NSTEMI patients	STEMI patients
CRP-0 hrs (mg/L)	3.32 ± 0.33	16.17 ± 5.45*	18.98 ± 5.05 *
CK-MB (ng/dl)	3.02 ± 0.29	54.61 ± 14.65 *	1.59±15.88*
Troponin-I (ng/dl)	0.06 ± 0.02	5.10 ± 1.26 *	9.96 ± 1.32 *
Cholesterol (mg/dl)	184.12 ± 5.89	200.50 ± 7.83	191.81± 6.00
Triglyceride (mg/dl)	196.17 ± 12.52	179.68 ± 14.71	221.62±31.29
LDL (mg/dl)	106.74 ± 4.89	122.16 ± 6.96	113.78± 5.54
HDL (mg/dl)	38.84 ± 1.26	40.95 ± 2.02	40.68 ± 1.28
Platelet count (/cmm)	$2.64 \times 10^5 \pm 12039$	$3.03 \times 10^5 \pm 17453$	$2.78 \times 10^5 \pm 5703$
Prothrombin Time (sec)	14.02 ± 0.32	18.91 ± 0.87 *	17.75±0.68
APTT (sec)	30.64 ± 0.98	33.31 ± 1.34 *	33.72± 0.98 *

UA: unstable angina; NSTEMI: non ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction; CRP: C-reactive protein; CK-MB: MB iso-enzyme of creatine kinase; LDL: low density lipoprotein cholesterol; HDL: high density lipoprotein cholesterol; APTT: activated partial thrmboplastin time; Values are expressed as Mean ± SEM; *, $p = <0.05$ vs UA; ($p <0.05$ is statistically significant). The values between NSTEMI and STEMI were non significant.

The increase in the CRP levels in patients of STEMI and NSTEMI versus UA is reported mainly due to myocardial necrosis and release of cytokines mediated CRP response. A limited increase in the CRP levels in patients with UA could be due to low grade myocardial necrosis by ischemia[24], the same is however not conformed in this study. The CRP release in patients with CHD is associated with the extent and severity of AS, inflammation of coronary vessels, inflammation related to the extant of myocardial ischemia, inflammation related to extent of myocardial necrosis and the amount and activity of the circulating pro-inflammatory cytokins like IL-6 and tumor necrosis factor (TNF)[25].

Liuzzo et al[26] have shown that during AMI, elevated levels of acute phase protein are not the result of myocardial cell necrosis. Moreover, the transient myocardial ischemia-reperfusion is unlikely to cause a detectable increase in CRP levels.

We identified significant correlation between plasma peak CRP levels and Troponin I concentration in patients with UA and NSTEMI. A significant correlation was also seen between the baseline levels of CK-MB and Trop I in patients of UA, NSTEMI and STEMI, while correlation between CRP levels and CK-MB concentration, PT and APTT was found to be non significant. These results are in consistence with Brunetti et al[27] who identified a positive correlation between peak CRP levels and Troponin I in patients with ACS. Beer et al[28] showed a significant correlation between plasma CRP levels and CK-MB in patients with AMI, while Speidl et al[29] showed no correlation between CRP levels and extension of necrotic area, number of coronary vessel with sever obstructive lesions and prognosis in the hospital.

The findings of this study that cigarette smoking, diabetes mellitus, positive family history of IHD and hypertension were more common and significant in patients with ACS versus controls. The results are in agreement with Rubins et al[30] who showed that the major coronary risk factors were more common in patients with STEMI compared to UA and NSTEMI. However, Perski et al[31] found smoking to be the most common and significant risk factor in young patients with CHD. This distinction may be due to inconsideration of low levels of HDL as being a major risk factor for AS by previous investigator or possible ethnic differences including obesity, physical inactivity, less alcohol consumption and increase hepatic TG lipase activity. Risk stratification of patients with ACS is pivotal for correct allocation of health resources and for maximizing the benefit of available treatment modalities[32].

CONCLUSION

The CRP levels were raised in patients with ACS, the plasma CRP levels did not show significant correlation with coronary markers, (CK-MB, Trop I) coagulation markers (PT, APTT) and lipid profile (cholesterol, triglyceride, HDL and LDL cholesterol).

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