C-reactive protein and acute coronary syndrome: correlation with traditional risk factors, diagnostic cardiac biomarkers, and ejection fraction

Tahir Ahmed Munir, M. Nasir Afzal, Habib-ur-Rehman, Rashid Ahmed

ABSTRACT

Objectives
To determine the serum levels of C-reactive protein (CRP) in patients with acute coronary syndrome (ACS) at the time of admission and its correlation with traditional risk factors, cardiac biomarkers, and ejection fraction.

Methods
Sixty nine age matched controls and 133 consecutive patients of ACS were studied. CRP levels, CK-MB and Trop-I were measured at 0, 12 and 24 hours of admission. Ejection fraction was estimated by bidimensional echocardiography.

Results
Mean CRP levels at the time of admission were significantly increased in patients of ACS versus controls and in patients of STEMI and NSTEMI versus UA, but were non significant between STEMI and NSTEMI patients. In patients of ACS, the cardiac biomarkers and the mean CRP levels during next 24 hours were increased significantly. A significant correlation between peak CRP levels and Trop I was seen in patients with UA and NSTEMI, but no correlation was found between CRP levels and CK-MB and ejection fraction.
**Conclusion**

CRP levels were increased in patients with ACS as compared to controls, and in patients of STEMI and NSTEMI as compared to UA. CRP levels did not correlate with EF but correlated with troponin I. (Rawal Med J 2009; 34: ).

**Keyword**

C - reactive protein, CRP, Acute coronary syndrome, ACS, STEMI, NSTEMI.

**INTRODUCTION**

Coronary heart disease (CHD) incidence is increasing in the developing countries. A number of predisposing factors affect the development of ischemic heart disease (IHD) and to date, more than 246 risk factors, including dyslipidemia and atherosclerosis (AS), have been identified. In patients with CHD, risk stratification is important, as information about probability of cardiovascular events in future can help target therapy. Several plasma markers of inflammation have been evaluated as potential tools for the prediction of the coronary events. These include, among others, serum amyloid A, IL-6, fibrinogen, homocysteine, apolipoprotein-A, apolipoprotein B-100 and C-reactive protein.

CRP is an acute phase reactant protein produced in the liver in response to injury, inflammation and acute infections, has an average half life of about 18 to 20 hours, and can be measured at any time of the day. The activation of acute phase response from infection, immune activation or injury is signaled by interleukin-6, which produces protein such as fibrinogen, CRP and serum amyloid A. CRP reflects the presence and intensity of inflammation and is now regarded as a surrogate marker and mediator of the atherothrombotic diseases. In a study comparing the magnitude of predictive value to twelve other putative risk factors, CRP was found to be a more predictable risk marker for
ACS and stroke than others. The elevated CRP levels correlate with the prognosis, irrespective of the extent of myocardial damage, and may reflect an important role of a pre-existing inflammation or a higher prevalence of myocardial necrosis and ischemic reperfusion damage. Studies have reported that CRP levels increase during acute myocardial infarction (AMI) and unstable angina but the changes that occur in the process of acute ischemic attack have been mainly studied in patients of non-ST segment elevation myocardial infarction (NSTEMI). The aim of the present study was to evaluate the CRP levels in patients with ACS (STEMI, NSTEMI, and UA) and its correlation with risk factors, cardiac biomarkers, and ejection fraction (EF).

**PATIENTS AND METHODS**

The study was carried out at the Shifa College of Medicine and Shifa International Hospital Islamabad and a total of 202 subjects; 69 controls and 133 patients of ACS, were studied. The variables included in the study were age, gender, traditional risk factors, Trop I, CK-MB, and CRP. The recorded traditional risk factors were hypertension, diabetes mellitus, cigarette smoking and family history of IHD in any first degree relative younger than 50 years who had angina or MI. The definitions of ACS and MI were as of American College of Cardiology and European Society of Cardiology. Patients with history of infection or inflammation during the last 15 days, or with hepatic and renal disease and those who did not sign the informed consent were excluded from the study. Venous blood drawn at time of admission (within 6 hours) was analyzed for CRP, CK-MB, Trop I, and at 12 and 24 hours after hospital admission for analysis of CRP. The plasma CRP levels were estimated with particle enhanced immunoturbidimetric method based on antigen-antibody reaction (Hitachi 911, Roche Diagnostic, Germany). CK-MB
and Trop I were determined by Microparticle Enzyme immuno-assay (MEIA) based on ‘sandwich’ principle (AxSYM system, Abbott Laboratories, USA). In all patients 2-D echocardiography was performed within 24 hours of admission with Nemio-30 device by Toshiba from Japan and biplane Simpson rule algorithm.

**Statistical Analysis:** 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**

The patients of ACS showed a highly significant difference in the percentage of diabetes mellitus, systolic and diastolic blood pressure, smoking, family history of IHD and hypertension as compared to controls. A highly significant difference was also seen in patients of UA, NSTEMI and STEMI versus controls in the percentage of DM, systolic and diastolic blood pressure, and smoking, while the percentage of family history of hypertension and family history of IHD was significantly increased in the patients of NSTEMI versus controls. At the time of admission, a statistically highly significant difference was seen in patients of ACS, STEMI and NSTEMI patients versus controls, when admission CRP, CK-MB, and Trop I were measured (Table 1).
Table 1. Clinical characteristics and traditional risk factors in patients with acute coronary syndrome and controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>ACS Patients</th>
<th>UA Patients</th>
<th>NSTEMI Patients</th>
<th>STEMI Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60 years</td>
<td>50.7%</td>
<td>55.6%</td>
<td>69.0%</td>
<td>39.5%</td>
<td>51.4%</td>
</tr>
<tr>
<td>Sex – Male</td>
<td>66.7%</td>
<td>63.2%</td>
<td>53.4%</td>
<td>65.8%</td>
<td>75.7%</td>
</tr>
<tr>
<td>DM</td>
<td>29.0%</td>
<td>62.4%*</td>
<td>56.9%**</td>
<td>55.3%†</td>
<td>78.4%††</td>
</tr>
<tr>
<td>Systolic HTN</td>
<td>2.9%</td>
<td>28.6%*</td>
<td>25.9%**</td>
<td>31.6%†</td>
<td>29.7%††</td>
</tr>
<tr>
<td>Diastolic HTN</td>
<td>4.3%</td>
<td>24.1%*</td>
<td>27.6%**</td>
<td>23.7%†</td>
<td>18.9%††</td>
</tr>
<tr>
<td>Smokers</td>
<td>15.9%</td>
<td>55.6%*</td>
<td>56.9%**</td>
<td>44.7%†</td>
<td>64.9%††</td>
</tr>
<tr>
<td>Family H/O IHD</td>
<td>18.8%</td>
<td>33.1%*</td>
<td>17.2%**</td>
<td>39.5%†</td>
<td>51.4%††</td>
</tr>
<tr>
<td>Family H/O HTN</td>
<td>24.6%</td>
<td>9.0%*</td>
<td>8.6%</td>
<td>7.9%†</td>
<td>10.8%</td>
</tr>
<tr>
<td>Family H/O DM</td>
<td>18.8%</td>
<td>19.5%*</td>
<td>17.2%**</td>
<td>26.3%</td>
<td>16.2%</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>3.2 ± 0.3</td>
<td>11.3 ± 2.1*</td>
<td>3.3 ± 0.3</td>
<td>16.2 ± 5.4</td>
<td>18.9 ± 5††</td>
</tr>
<tr>
<td>CK-MG (ng/dl)</td>
<td>2.6 ± 0.2</td>
<td>39.6 ± 6.7*</td>
<td>3.0 ± 0.3</td>
<td>54.6 ± 14.6</td>
<td>81.6 ± 15††</td>
</tr>
<tr>
<td>Trop I (mg/dl)</td>
<td>0.09 ± 0.03</td>
<td>4.2 ± 0.62*</td>
<td>0.06 ± 0.02</td>
<td>5.1 ± 1.26</td>
<td>9.9 ± 1.3††</td>
</tr>
</tbody>
</table>

Values are expressed in percentage and mean ± SEM; * ** † †† p = <0.05 vs. controls.

When the cardiac biomarkers, CK-MB, Trop I, and CRP at 0, 12 and 24 hours were compared, a highly significant difference was seen in patients of NSTEMI and STEMI versus UA. However, the levels between patients of STEMI and NSTEMI were found to be non significant (Table 2).

Table 2. Clinical characteristics within the patients of acute coronary syndrome

<table>
<thead>
<tr>
<th></th>
<th>UA patients</th>
<th>NSTEMI patients</th>
<th>STEMI patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP-0 hrs (mg/L)</td>
<td>3.32 ± 0.33</td>
<td>16.17 ± 5.45*</td>
<td>18.98 ± 5.05 **</td>
</tr>
<tr>
<td>CRP-12 hrs (mg/L)</td>
<td>5.32 ± 0.58</td>
<td>30.03 ± 6.63 *</td>
<td>38.24 ± 6.31 **</td>
</tr>
<tr>
<td>CRP – 24 hrs (mg/L)</td>
<td>6.87 ± 0.77</td>
<td>45.22 ± 8.76 *</td>
<td>62.81 ± 10.20 **</td>
</tr>
<tr>
<td>CK-MB (ng/dl)</td>
<td>3.02 ± 0.29</td>
<td>54.61 ± 14.65 *</td>
<td>81.59 ± 15.88 **</td>
</tr>
<tr>
<td>Tropinin-I (ng/dl)</td>
<td>0.06 ± 0.02</td>
<td>5.10 ± 1.26 *</td>
<td>9.96 ± 1.32 **</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>49.19 ± 1.59</td>
<td>48.87 ± 1.80</td>
<td>46.68 ± 1.95</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SEM; * ** p = <0.05 vs. UA; the values between NSTEMI and STEMI were non significant.

During hospital stay for next 24 hours, mean CRP levels at 12 hours were found to be raised significantly in the patients of UA, NSTEMI and STEMI as compared to at 0 hours.
Similarly, when the levels at 24 hours were compared with levels at 12 hours, a highly
significant difference was found in patients of UA, NSTEMI and STEMI (Fig. 1).

<table>
<thead>
<tr>
<th></th>
<th>CRP in mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hr</td>
</tr>
<tr>
<td>UA</td>
<td>3.32</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>16.17</td>
</tr>
<tr>
<td>STEMI</td>
<td>18.98</td>
</tr>
</tbody>
</table>

**Fig.1. Mean CRP levels with time course in patients with UA, NSTEMI and STEMI.**

Values expressed are Mean ± SEM; p = <0.05 vs. 0 hours in patients with UA, NSTEMI and STEMI; p = <0.05 vs. 12 hours in patients with UA, NSTEMI and STEMI

In the patients of UA, a significant correlation was seen between Trop I concentration and
mean CRP levels at 12 hours (r = 0.514, p = 0.000) and at 24 hours of admission (r = 0.489,
p = 0.000) (Fig.2).
Fig. 2. Correlation between peak (24 hours) plasma CRP levels and Trop I concentration in patients with unstable angina; CRP: \( r = 0.489, p = 0.000 \).

Correlation between baseline Trop I and CK-MB in patients of STEMI was found to be statistically significant \( r = 0.714, p = 0.000 \). A positive correlation was also seen between baseline Trop I and CK-MB levels in patients with UA \( r = 0.342, p = 0.009 \) and NSTEMI patients \( r = 0.908, p = 0.000 \). However, the correlation between peak CRP levels, EF and baseline CK-MB concentration were found to be non significant.

**DISCUSSION**

The present study showed that the plasma CRP levels were significantly increased in patients of ACS at time of admission as compared to controls. These results are consistent with Tomado et al\textsuperscript{14} and Gavusoglu et al,\textsuperscript{15} who demonstrated increased CRP levels in patients with ACS within 6 hours of admission. Our results showed a significant difference of mean CRP levels in patients of NSTEMI, STEMI as compared to UA patients and are in consistence with Zebrack et al\textsuperscript{11} and Kazmierezak et al,\textsuperscript{16} who identified increase in the
CRP levels in patients of STEMI and NSTEMI versus UA, 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, which is, however, not confirmed in this study.

Our results showed that the CRP levels increase with the passage of time after hospital admission in patients with ACS and are in agreement with earlier reports. A possible reason may be myocardial necrosis and the ischemia reperfusion injury. The plasma peak levels of CRP reach peak within about 48 hours, and with abrupt cessation of the stimulus, the values then decrease exponentially at a rate close to the measured plasma half life of CRP at about 19 hours. Liuzzo et al have shown that during AMI, elevated levels of acute phase protein are not the result of myocardial cell necrosis, and 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 was found to be non significant. These are consistent with Brunetti et al, who reported a positive correlation between peak CRP levels and Troponin I in patients with ACS. Beer et al showed a significant correlation between plasma CRP levels and CK-MB in patients with AMI, while Speidl et al showed no correlation between CRP levels and extension of necrotic area, number of coronary vessels with severe obstructive lesions, and prognosis in the hospital. Our results are in agreement with Rubins et al, who showed that the major coronary risk factors were more common in patients with STEMI compared to UA and NSTEMI.
However, Perski et al\textsuperscript{24} found smoking to be most common and significant risk factor in young patients with CHD.

**CONCLUSION**

Our study showed that CRP levels were raised in patients with ACS at time of admission, and further increased with the passage of time during hospital stay. The plasma CRP levels also showed significant correlation with Trop I concentration in patients with ACS. However, the correlation with CK-MB and ejection fraction, was found to be non significant. CRP can complement the present clinical and laboratory parameters used as guides in the optimal management of patients with IHD.

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