C-REACTIVE PROTEIN AND ACUTE CORONARY SYNDROME: COMPARISON OF CONSERVATIVE AND INTERVENTIONAL MANAGEMENT

Tahir Ahmad Munir, M. Nasir Afzal
Section of Physiology, Shifa College of Medicine, Islamabad

Background: Inflammation plays a key role in the initiation and progression of atherosclerosis, the most common cause of acute coronary syndrome. C-reactive protein (CRP) that enhances plaque inflammation is synthesized six hours after myocardial infarction. 

Methods: High sensitivity C-reactive protein was measured by Immunoturbiditory method in 50 healthy controls and 100 patients of acute coronary syndrome on conservative or interventional management.

Results: Serum C-reactive protein levels [mg/L ± SEM] at the time of admission were significantly raised in patients of acute coronary syndrome (11.90 ± 2.30) as compared to controls (2.30 ± 0.18) and further increased progressively during 24 hours of follow up period. C-reactive protein levels also increased significantly in patients who underwent interventional management (115.90 ± 7.73) as compared to those who were on conservative management (22.28 ± 5.54).

Conclusion: Serum C-reactive protein levels were found to be significantly raised in patients with acute coronary syndrome as compared to controls. In addition, patients undergoing interventional management had higher C-reactive protein levels, post intervention, as compared to those on conservative management.

Key Words: Acute Coronary Syndrome; Inflammation; C-Reactive Protein.

INTRODUCTION

Ischemic Heart Disease (IHD) is the most common cause of death in the developed world. Its incidence is also increasing rapidly in many developing countries and is expected to become major cause of death in all regions of the world 1. A number of predisposing factors affect the development of IHD and to date more than 246 risk factors have been identified 2. Acute Coronary Syndrome (ACS) is defined as Myocardial Infarction (MI) with ST segment elevation, MI without ST segment elevation and unstable angina, mostly induced by local coronary thrombosis as an acute complication of atherosclerosis (AS) 3. With growing evidence that atherosclerosis is an inflammatory process, several plasma markers of inflammation have been evaluated as potential tools for the prediction of coronary events 4. These markers of inflammation include Serum Amyloid-A, Interleukin-6, Homocysteines, Fibrinogen levels, Fibrinolytic capacity, Apolipoprotein-A, Apolipoprotein B-100, Lipoprotein (a) and C-reactive protein (CRP) 5.

CRP, the first acute phase reactant protein, is produced by the liver in response to injury, inflammation or acute infection 6. CRP was discovered in 1930 during the exploration of human inflammatory responses 7 but its role in heart disease has only recently been uncovered 8. CRP derives its name because of its ability to bind to the C polysaccharide of pneumococcal cell wall 9. This hepatically derived pentraxin has an average half life of about 18 to 20 hours and can be measured at any time of the day. A strong predictive value of CRP is because of its long term storage stability, lack of diurnal variation and no dependence on age or sex 9.

Levels of CRP are elevated in systemic inflammatory diseases such as lupus, acute appendicitis, and neonatal sepsis with values as high as 100 µg/ml or even higher but this has no specificity in differentiating various disease entities from one another 10. CRP also serves as a risk factor for IHD as an association between CRP and coronary events is becoming very evident. In a study, comparing the magnitude of predictive value to twelve other putative risk factors, CRP was found to have a higher predictive value for ACS and Stroke than other markers 11. Recent data also indicates that CRP is a better predictor of heart disease than Nuclear Magnetic Resonance based evaluation of LDL particle size and concentration 12. Multiple studies have shown that the CRP levels increase in patients with ACS 13,14 and also post intervention stent implantation or coronary artery bypass graft 15. But, no such study has been conducted in the Pakistani populations.

The present study has been designed to determine the levels of serum CRP in patients with ACS and to compare the levels of CRP between patients on conservative and interventional management. Results of this study will help us understanding various treatment modalities and resource allocation in patients with ACS in tertiary care hospitals in Pakistan.
MATERIAL AND METHODS

This case control study was carried out at the Shifa College of Medicine and Shifa International Hospital Islamabad. 150 subjects were included in this study, which were divided into 3 groups. Group A comprised of age matched healthy controls, group B patients with ACS (AMI & unstable angina) on conservative management while group C, included patients of ACS on interventional management. All patients were evaluated by detailed history, complete physical examination and relevant laboratory investigations to document the presence of ACS. Patients from both sexes who were more than 20 years of age with typical history of chest pain and ST elevation or depression of more than 0.1 mV in two consecutive ECG leads, or clinical picture of unstable angina were included. Patients with history of infection or inflammation during the last 15 days, hepatic, renal, or heart failure or history of previous MI and who expired in the hospital during their stay were excluded from the study. All the patients/relatives signed the informed consent form.

Venous blood under aseptic conditions was withdrawn from the patients at the time of admission. The blood samples were shifted to a tube and clotted at room temperature. The tubes were centrifuged for 5 minutes and the serum was separated for analysis of CRP, CK-MB and Trop I. The serum collected during follow up at 12 and 24 hours after admission from patients of group B and C and at 12, 24, and 72 hours after intervention from group C was stored at -20ºC till further analysis of CRP.

CRP levels were determined with Immunoturbidimetric method using the Hitachi 911 from Roche Diagnostics Germany and CK-MB and Troponine I by Microparticle Enzyme Immunoassay method using the AxSYM system from Abbott Laboratories USA.

All patients were treated with anti-ischemic, anti-platelets and anti-thrombotic drugs, while patients on interventional management underwent percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).

Data and results of the study were analyzed by SPSS version 10.0.

The protocol was approved by the institutional review board / Ethics committee Shifa College of Medicine.

RESULTS

Comparison of base line characteristics and various risk factors of coronary artery disease in patients of acute coronary syndrome and healthy controls are shown in Table 1. Percentage of males was relatively higher in patients on ACS as compared to controls.

History of smoking and family history of IHD was also higher in patients of ACS in comparison with healthy controls.

Cardiac biomarkers, CK-MB and Trop I were measured during clinical evaluation of patients of ACS at the time of admission. Both of these markers were significantly increased in patients of ACS as compared to controls (Table 2) confirming myocardial cell death and necrosis of myocardium.

CRP, an acute phase reactant serum protein measured in mg/L, at the time of admission was significantly increased in patients of ACS as compared to controls (Table 3). Follow up, of patients of ACS for next 24 hours during hospital admission showed a gradual increase in the serum levels of CRP (Figure 1). This increase was relatively more in patients on conservative management as compared to those who received interventional management (Figure 1).

Those patients who went through interventional management were followed for next 72 hours and showed significant increase in CRP levels in 24 hours and leveled off in next 72 hours (Figure 2).

Further analysis of the data revealed that mean CRP levels in patients on interventional management were significantly increased as compared to patients on conservative management (Figure 3).

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<th>Table 1- Demographic comparison between the study groups</th>
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<td>A†</td>
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<tr>
<td>Number</td>
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<tr>
<td>Mean Age (yr)</td>
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<tr>
<td>Sex (M/F %)</td>
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<td>Hypertension (n%)</td>
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<td>Smoking (n %)</td>
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<td>Family history of IHD (n %)</td>
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† Healthy Control subjects, * Patients of ACS on conservative management, • Patients of ACS on interventional management, IHD=Ischemic Heart Disease, n=Number, % Percentage, Yr=Year

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<th>Table 2- Plasma levels of CK-MB and Trop – I at the time of hospital admission in study groups</th>
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* p = <0.05 compared to controls – group A.
† p = <0.005 compared to patients on interventional management – group C.

CK-MB = Creatine Kinase MB Fraction, Trop I = Troponin I, A= Control Group, B= Patients on conservative management, C=Patients on interventional management.
Table 3: Comparison of CRP levels in study groups

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<th>CRP in mg/L</th>
<th>Group A</th>
<th>Group B + C</th>
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<td>2.34 ± 0.18</td>
<td>7.53 ± 1.23</td>
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Group A = Control Group, Group B + C = Patients of ACS,
+ p = 0.003 compared to controls
CRP = C-reactive protein

**DISCUSSION**

Results of the present study illustrate that CRP was significantly raised in patients with ACS (AMI or unstable angina) shortly after the onset of the symptoms. The acute-phase response of CRP is a nonspecific phenomenon reflecting cytokine-mediated hepatic production, triggered by most forms of inflammation, infection and tissue injury. Our patients were carefully selected to eliminate intercurrent disorders likely to be associated with an acute-phase response.

Auer J 16 and his colleagues had shown that CRP levels do not increase at the time of hospital admission till 6-12 hours after the onset of symptoms in patients of ACS. It was suggested by them that affected coronary vessels are small and the total number of activated macrophages involved in unstable coronary plaques are too small to be detected by increased peripheral serum CRP concentration.

Our results and results from Tomado H et al 17 and Gavusoglu Y et al 18 demonstrated that the CRP levels in patients with ACS (AMI and unstable angina) at the time of admission (within 6 hours) were significantly higher as compared to controls. The increased CRP levels at the time of admission, also corresponded with an increase in the white blood cell count 19, serum neopterin levels 20, release of pro-inflammatory cytokines and increased urinary concentration of leukotriene E4 21, all indicators of acute inflammation.

The inflammatory process has been shown to be one of the mechanisms causing plaque rupture that leads to increased CRP levels in less than 6 hours in patients with ACS 22. The CRP levels within 6 hours after the onset of AMI is suggested to offer valuable information with respect to cell biology activity of the ruptured plaque without being affected by the effects of myocardial damage in the form of necrosis. The CRP levels in AMI, of onset greater than or equal to 6 hours are due to the result of myocardial damage. Previous studies have demonstrated that circulating concentration of human CRP increases approximately 6 hours after onset of symptoms and reach a peak after 40-50
hours. Therefore, according to our study and other studies, serum CRP may be categorized into two different intervals in the clinical setting of AMI. This finding may be of clinical importance because it may provide useful information for assessment of possible impact of CRP levels on coronary atherosclerotic lesions and clinical outcomes of patients with AMI undergoing various modes of managements.

Recently, Tomoda and Aoki tried to find a correlation between the serum levels of CRP and the vulnerability of the culprit coronary lesion within 6 hour of onset of AMI. They demonstrated that patients with elevated CRP levels on hospital admission had more vulnerable coronary artery lesions and worse clinical outcomes than patients with normal serum CRP levels. However, this retrospective study did not do a comparison between risk control and healthy control subjects. Therefore, this could not correlate different levels of serum CRP among patients with AMI of onset \( \leq \) 6 hour, risk control subjects, and normal subjects.

Tomoda and Aoki further suggest that significantly increased CRP or a spike in serum CRP may be fundamentally important prerequisite for an atherosclerotic plaque to rupture, which as a consequence may lead to AMI. CRP also correlates with the number of vulnerable atherosclerotic plaques with large necrotic cores and thin fibrous cap atheroma. 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.

An autopsy study from Burke et al. demonstrated that there is a strong correlation between CRP levels and increased numbers of thin atheromas in the coronary tree. Moreover, a positive correlation between the intensity of CRP staining in plaque and serum levels of CRP was also found in their study. Many patients with unstable angina have also raised CRP levels at the time of admission.

The results of our study are also consistent with Auer J et al. who showed that CRP is elevated with the time course after hospital admission in patients of ACS. Plasma levels of CRP reach a 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. In our study the lowest levels were observed at base line (time of admission) and were significantly different from the levels measured during the following 24 hours with the possible reason of myocardial cell necrosis and ischemia-reperfusion injury.

Liuzzo G et al. 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.

The coronary artery occlusion results in myocardial ischemia, and if blood flow is not restored within a reasonable time, infarction results. After coronary occlusion, restoration of blood flow which contributes to injury and the tissue damage is termed reperfusion injury. Experimental studies have shown that the periods of ischemia as short as 15 minutes followed by reperfusion elicits a cascade of pro-inflammatory reactions that include production of \( \text{O}_2^\bullet \) derived free radicals, activation of complement system via the alternative as well as the classical pathway, adherence of neutrophils to the coronary endothelium, leukocyte-mediated injury of the myocardial cells and the production of cytokines including IL-6, IL-1, which are the major determinants of the acute phase protein production.

In our study, one group of patients was on conservative management (group B) while the other was on interventional management (group C). Our results demonstrate that the CRP levels were significantly increased in patients with ACS on interventional management after intervention (PCI with stenting and CABG) as compared to patients on conservative management and controls. Margalet VS et al. and Liuzzo et al. demonstrated that stenting triggers a quantitatively high inflammatory response by inflammatory markers, detected by measuring various markers at different time intervals. Percutaneous Transmural Coronary Agioplasty (PTCA) has been shown to cause plaque rupture, arterial wall damage and release of inflammatory factors that may result in systemic inflammatory response.

Patients of our study, who underwent interventional management were mostly the cases of unstable angina and had low CRP levels as compared to patients of AMI. On the basis of our study it could be suggested that patients having low CRP levels are better treated by interventional management rather than by conservative management, but further studies may be required to prove that.

**Limitations of Study**

Effect of myocardial damage on serum CRP could not be completely evaluated in the present study because exact time of onset of symptoms was usually difficult to determine in our patients. Therefore, a potentially inaccurate duration from onset of AMI to blood sample could be present.

Our study was not designed to investigate the correlation between serum CRP and short or long
term clinical outcomes. Therefore, we could not provide evidence other than serum levels of CRP in the clinical setting of AMI. We did not know whether elevation of CRP within 6 hours was chronic and persistent or only reflected a surge episode.

CRP levels are higher in patients with AMI/unstable angina as compared to controls. The possibility could not be ruled out whether observed difference would reach significant level if much larger patients groups would have been included.

The observation of our study may be confirmed in future by serum amyloid A protein because it has an even wider dynamic range.

**CONCLUSIONS**

The data of our study suggests an activation of the inflammatory system in patients with AMI or unstable angina, reflected by increased CRP levels. The chronic inflammatory process during stable atherosclerotic disease and initial period of plaque instability with involvement of inflammatory cells induces CRP production that reaches to statistically significant levels at the time of admission in patients of ACS within 6 hours. CRP does not represent a marker for the extent of myocardial damage but indicates inflammation associated with myocardial damage. CRP at the time of admission may be a valid prognostic marker but may not be suitable for distinguishing between non cardiac and cardiac pain in patients with ACS. Finally, the CRP levels also increase significantly in patients who undergo invasive management like PCI / CABG as compared to those who receive conservative treatment.

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Address for Correspondence: Dr. Tahir Ahmad Munir, Section of Physiology, Shifa College of Medicine, H/8, Islamabad - 44000. Phone: 92-51-444-6801-ext 3390, Fax No. 92-51-4435046
E-mail: tahirahmadmunir1@hotmail.com