## Relationship of high sensitivity C-reactive protein with Cardiac Biomarkers in patients presenting with Acute Coronary Syndrome

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Short Running Title: hsCRP & ACS

**Abstract**

**Objective:** The aim of this study was to determine high sensitivity c reactive protein (hsCRP) levels in patients with acute myocardial infarction (AMI) and see its correlation with classical enzyme markers of myocardial damage.

**Design:** Observational study.

**Place and Duration of Study:** Department of emergency medicine at King Khalid University Hospital, King Saud University, Riyadh and department of Physiology from August 2010 to December 2011.

**Methodology:** Consecutive eligible patients with either ST elevation myocardial infarction (STEMI) or non ST elevation myocardial infarction (NSTEMI) who were admitted at emergency department of King Khalid University Hospital were recruited. A total of 71 subjects were finally selected for the study. The hsCRP, Troponin I (Trop I), Creatine kinase myocardial bound (CK-MB), Aspartate aminotransferase (AST) and Lactate dehydrogenase (LDH) concentrations of all patients with an acute myocardial infarction (AMI) were measured.

**Results:** Among all patients 34 (47.9%) patients had diabetes mellitus, 21 (29.6%) were hypertensive, and 16 (22.5%) had no associated illness. Patients with STEMI had significantly higher levels of CKMB (p=0.0348), LDH (p=0.0471) and hsCRP (p=0.0231) compared to NSTEMI patients. While the differences were non significant for TropI (p=0.7022), AST (p=0.9729) and Lp(a) (p=0.5985). Spearman’s correlations revealed that CRP correlated significantly with TropI, CK-MB and LDH. There was a significant predictive relationship of hsCRP with TropI, LDH and CK-MB while with AST it was non significant.

**Conclusion:** hsCRP levels is a significant predictor of standard markers for myocardial damage and it may be a useful prognostic marker in acute coronary syndromes.

**Key Words:** C-Reactive Protein; Acute Myocardial Infarction; Acute Coronary

Syndrome; Inflammation, creatine kinase myocardial bound.

**INTRODUCTION**

Evidence suggests that inflammation plays a key role in the pathogenesis of atherosclerosis. The chronic inflammatory process can develop to an acute clinical event by the induction of plaque rupture and therefore cause acute coronary syndromes [1]. Auer J et al reported that baseline CRP levels in the subgroup of patients with AMI were significantly higher than in patients with stable CAD [2]. CRP levels predict future cardiovascular events independently of CAD severity and correlate with number of angiographically complex coronary artery stenosis in patients with ACS. Thus, CRP levels are a marker of atheromatous plaque vulnerability and CAD activity [3]. No significant correlation was found between baseline CRP serum levels and angiographic measures of atherosclerotic disease severity and extent. In patients with unstable angina, CRP serum levels and coronary atherosclerosis are not correlated, but both are independently associated with a worse outcome at follow-up [4]. Myoglobin, the smallest of all markers, diffuses rapidly in the vascular system and quickly gives indication for a possible acute myocardial infarction (AMI). Myoglobin levels increase within 0.5 -2 hours from the onset of chest pain, reach peak values at 5-12 hours. Normal circulatory concentration might be detected after 16-36 hours [5,6]. CK-MB is one of the most important myocardial markers, and it is an established marker in confirmation of AMI. In AMI plasma concentration of CK-MB is increased within 3-8 hours of onset of chest pain, the peak is reached within 9-30 hours and return to baseline levels after 48-72 hours [7,8,9]. Currently, it is of critical importance to reduce the time between the onset of chest pain and hospital admission. What is of great importance is determining the most sensitive and useful marker , helpful in finding the best, most effective treatment of the patients with ACS. The aim of this study was to determine high sensitivity c reactive protein (hsCRP) levels in patients with acute myocardial infarction (AMI) and see its correlation with classical enzyme markers of myocardial damage.

**METHODS**

This observational study was conducted at the departments of emergency medicine, physiology and cardiology of college of medicine & King Khalid university hospital, King Saud University, Riyadh, Saudi Arabia from August 2010 to December 2011. Consecutive eligible patients with either STEMI or NSTEMI who were admitted at King Khalid University Hospital were recruited. A total of 71 patients (46 Males & 25 Females) were finally selected for the study. The hsCRP, Troponin I (Trop I), Creatine kinase myocardial bound (CKMB), Aspartate aminotransferase (AST) and Lactate dehydrogenase (LDH) concentration of these patients with an acute coronary syndrome (ACS) were measured after admission and their peak levels were recorded. Inclusion criteria included patients of any sex with both non-ST elevation acute coronary syndrome and ST elevation acute coronary syndrome. The diagnosis of myocardial infarction required the presence of at least 2 of these criteria (1) A history of characteristic prolonged ( ≥ 30 min) pain or discomfort (2) Creatine kinase (CK) elevation exceeding twice the upper limit of normal (or CK-MB ≥ 50% of total CK). Presence of new Q waves or new abnormal ST-T features [10]. Patients with STEMI were required to have: (1) continuous chest pain upon presentation, refractory to nitrates, and lasting ≥ 30 min; (2) ST-segment elevation of ≥ 0.2mV in ≥ 2 contiguous precordial leads, or ≥ 0.1mV in ≥ 2 contiguous limb leads, or new (or presumably new) left bundle branch block on admission electrocardiogram; (3) presentation within the first 12 h from index pain. Patients with NSTEMI were required to have angina-like chest pain at rest in the last 24 h lasting ≥ 5 min, with associated STsegment depression of ≥ 0.1mV in ≥ 2 contiguous leads upon presentation [11]. Patient with (1) angina of secondary etiology, (2) recent surgery, (3) active infection, or chronic inflammatory diseases (thyroid disorders, acute infections, stroke, diabetic ketoacidosis, non-ketotic hyperosmolar diabetes, rheumatic diseases, chronic liver diseases, renal disorders, cancer and sepsis), (4) significant hepatic or renal dysfunction, and (5) malignancy, were not included as well as (6) individuals with body temperature of >37.8°C at admission, (7) those who had suffered a coronary or cerebral event in that same period, those with complete left bundle block, those with pacemaker rhythm, and those with serious aortic valve disease, obstructive hypertrophic cardiomyopathy, and subjects who were critically ill or with ongoing or recent (< 1 month) infectious diseases (8) patients with surgical procedures in last 3 months were excluded. We followed the guidelines of the American Heart Association for measurement, evaluation and expression of hsCRP [12]. Fasting venous blood samples were analyzed for lipid levels, comprising total cholesterol (TC), Triglycerides (TG), Low density Lipoprotein (LDL) and High density lipoprotein (HDL). TC, TG, LDL and HDL were analyzed by an enzymatic colorimetric method. The equipment used was a Dimension autoanalyzer (USA) and the kits were also provided by the same company. Levels of hsCRP and Lp(a) were measured by turbidimetric assays with commercial kits (Quantex Lp(a) supplied by BIOKIT, S.A., Barcelona, Spain) on a Hitachi 911 equipment (ROCHE diagnostics, USA). The kit had a working range from 0.10 to 20.0 mg/L for hsCRP. For Lp(a) the Limit of Quantification (LOQ) was 1.3 mg/dL and the Limit of Detection (LOD) was 0.4 mg/dL. The autoanalyzer used was Hitachi 911, manufactured by ROCHE diagnostics, USA.

**Statistical Analysis**

The data were analyzed by the computer software program Statistical Package for Social Sciences (SPSS version 10, Chicago). Descriptive characteristics and the lipid profile of the study patients were calculated as Mean ± SD (Standard Deviation) with median and range values. Kolmogorov-Smirnova andShapiro-Wilk tests were used to see that data is following normal distribution or not. Those parameters which were not following normal distribution were analyzed by non parametric tests.

Student’s t test was used to assess differences in age, blood pressure, TC, LDL, HDL, TG and BMI. Data on hs- CRP, Lp(a) and cardiac enzymes, because of their extreme skewness, were analyzed by non-parametric Mann-Whitney U test. Relationship of CRP levels with cardiac enzymes was determined by Spearman’s correlation analysis. Linear regression analysis was also performed to see the predictive relationship between hsCRP with cardiac enzymes in AMI patients. A p value of <0.05 was considered statistically significant.

**RESULTS**

This study shows relationship of inflammatory marker hsCRP levels with cardiac enzymes in patients with AMI. Table 1 shows descriptive characteristics, Lipid, Lp(a) and Peak cardiac enzyme levels levels of all study subjects with their ranges. Among all patients 34 (47.9%) patients had diabetes mellitus, 21 (29.6%) were hypertensive, and 16 (22.5%) had no associated illness. Fifteen patients (21.1%) were smokers. Patients with AMI were divided into STEMI and NSTEMI groups. Comparison of Descriptive characteristics and Lipid levels between STEMI & NSTEMI patients is expressed in Table 2. It was observed that all differences were non significant. When we compared the cardiac enzymes, hsCRP and Lp(a) levels between the two groups [Table 3]. We observed that the patients with STEMI had significantly higher levels of CKMB (p=0.0348), LDH (p=0.0471) and hsCRP (p=0.0231) compared to NSTEMI patients. While the differences were non significant for TropI (p=0.7022), AST (p=0.9729) and Lp(a) (p=0.5985). Spearman’s correlation analysis showed that hsCRP levels correlated significantly with TropI, CK-MB and LDH. Therefore, Linear regression analysis was performed to see the relationship between hsCRP, TropI, CK-MB, AST and LDH values in AMI patients (Figure 1 (a), (b) (c)). There was a significant predictive relationship of CRP with TropI, LDH and CK-MB while with AST it was non significant.

**Table 1: Descriptive characteristics, Lipid, Lp(a) and Peak cardiac enzyme levels levels of all study subjects.**

|  | Mean ± SD | Median | Minimum | Maximum |
| --- | --- | --- | --- | --- |
| Age (years) | 54.66 ± 11.79 | 54.00 | 18.0 | 80.0 |
| Height (cm) | 165.39 ± 8.02 | 168.00 | 144.0 | 179.0 |
| Weight (kg) | 80.59 ± 15.30 | 80.00 | 55.0 | 112.0 |
| BMI | 29.50 ± 5.23 | 28.82 | 18.84 | 43.79 |
| Pulse Rate | 83.78 ± 16.06 | 80.00 | 49.0 | 132.0 |
| SBP mmHg | 127.98 ± 19.36 | 130.00 | 74.0 | 167.0 |
| DBP mmHg | 76.86 ± 13.93 | 75.00 | 42.0 | 114.0 |
| Temp oC | 36.54 ± 0.59 | 36.50 | 35.6 | 38.9 |
| Lp(a) mg/dl | 23.64 ± 21.24 | 17.20 | 3.10 | 96.1 |
| TC mmol/L | 4.40 ± 1.29 | 4.50 | 1.90 | 6.81 |
| TG mmol/L | 1.83 ± 0.88 | 1.64 | 0.48 | 3.79 |
| LDL mmol/L | 2.65 ± 1.11 | 3.03 | 1.46 | 4.84 |
| HDL mmol/L | 0.77 ± 0.20 | 0.78 | 0.50 | 1.24 |
| Trop I IU/L | 3.72 ± 5.64 | 0.40 | 0.001 | 18.69 |
| CKMB IU/L | 31.23 ± 23.22 | 24.00 | 1.0 | 92.0 |
| AST IU/L | 117.13 ± 157.07 | 55.50 | 17.0 | 878.0 |
| LDH IU/L | 309.46 ± 157.97 | 256.00 | 117.0 | 774.0 |
| CRP mg/L | 1.37 ± 1.60 | 0.50 | 0.05 | 4.19 |

Data is expressed as Mean ± SD

Body mass index (BMI), Systolic blood pressure (SBP), Diastolic Blood pressure (DBP).

Lipoprotein (a) [Lp(a)], Total cholesterol (TC), Triglycerides (TG), Low density Lipoprotein (LDL) and High density lipoprotein (HDL).

**Table 2: Comparison of Descriptive characteristics and Lipid levels**

**between STEMI & NSTEMI patients**

|  | **NSTEMI**  **n=27** | **STEMI**  **n=44** | **p-value** |
| --- | --- | --- | --- |
| Male/Females | 16/11 | 30/14 |  |
| Age (years) | 56.28 ± 12.90 | 53.65 ± 11.09 | 0.3857 |
| Height (cm) | 165.11 ± 9.07 | 165.54 ± 7.57 | 0.8549 |
| Weight (kg) | 78.84 ± 18.67 | 81.53 ± 13.39 | 0.5401 |
| BMI | 28.87 ± 5.68 | 29.81 ± 5.06 | 0.5489 |
| Pulse Rate | 84.22 ± 16.10 | 83.50 ± 16.25 | 0.8688 |
| SBP mmHg | 124.96 ± 17.64 | 129.92 ± 20.38 | 0.3415 |
| DBP mmHg | 76.04 ± 12.41 | 77.39 ± 14.97 | 0.7208 |
| Temp oC | 36.42 ± 0.50 | 36.63 ± 0.64 | 0.1916 |
| TC mmol/L | 4.22 ± 1.52 | 4.51 ± 1.15 | 0.4143 |
| TG mmol/L | 1.68 ± 1.04 | 1.92 ± 0.79 | 0.3147 |
| LDL mmol/L | 2.53 ± 1.21 | 2.74 ± 1.06 | 0.5250 |
| HDL mmol/L | 0.72 ± 0.19 | 0.80 ± 0.20 | 0.1492 |

Lipoprotein (a) [Lp(a)], Total cholesterol (TC), Triglycerides (TG), Low density Lipoprotein (LDL) and High density lipoprotein (HDL).

Data is expressed as Mean ± SD

**Table 3: Comparison of peak cardiac enzyme levels, Lp(a) and hsCRP levels between STEMI & NSTEMI patients.**

|  | **NSTEMI**  **n=27** | **STEMI**  **n=44** | **p-value** |
| --- | --- | --- | --- |
| Trop I IU/L | 0.02 (7.60) | 1.21 (5.54) | 0.7022 |
| CKMB IU/L | 15.00 (14.00) | 30.00 (31.75) | 0.0348 |
| AST IU/L | 53.50 (148.00) | 55.75 (100.00) | 0.9729 |
| LDH IU/L | 145.00 (200.50) | 255.00 (199.75) | 0.0471 |
| CRP mg/L | 0.17 (0.86) | 0.81 (2.63) | 0.0231 |
| Lp(a) mg/dl | 16.60 (27.70) | 20.02 (18.43) | 0.5985 |

Troponin I (Trop I), Creatine kinase myocardial bound (CKMB), Aspartate aminotransferase (AST), Lactate dehydrogenase (LDH), Lipoprotein (a) [Lp(a)],

Data is expressed as Median(Inter Quartile Range)

**Table 4: Spearman’s correlation between CRP, TropI, CK-MB, AST and LDH.**

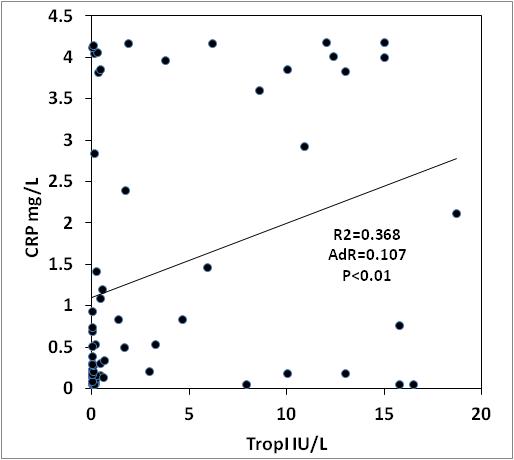
|  | TropI | CKMB | AST | LDH | CRP |
| --- | --- | --- | --- | --- | --- |
| TropI | 1.000 | .208 | .166 | .287\* | .368\*\* |
| CKMB | .208 | 1.000 | .522\*\* | .393\*\* | .405\*\* |
| AST | .166 | .522\*\* | 1.000 | .475\*\* | .151 |
| LDH | .287\* | .393\*\* | .475\*\* | 1.000 | .487\*\* |
| CRP | .368\*\* | .405\*\* | .151 | .487\*\* | 1.000 |

\*\*. Correlation is significant at the 0.01 level.

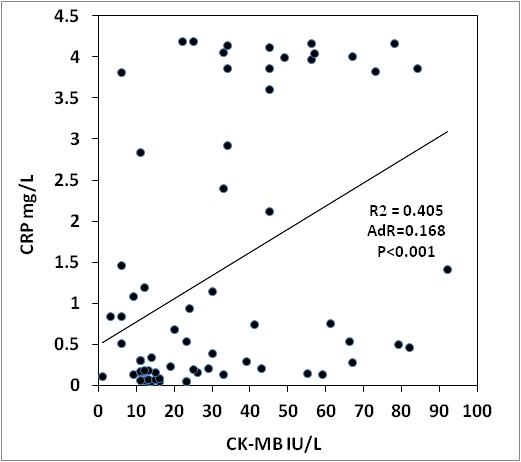
\*. Correlation is significant at the 0.05 level.

**Figure 1: Linear regression analysis between hsCRP levels and TropI (a), LDH (b) and CK-MB (c) levels in AMI patients.**

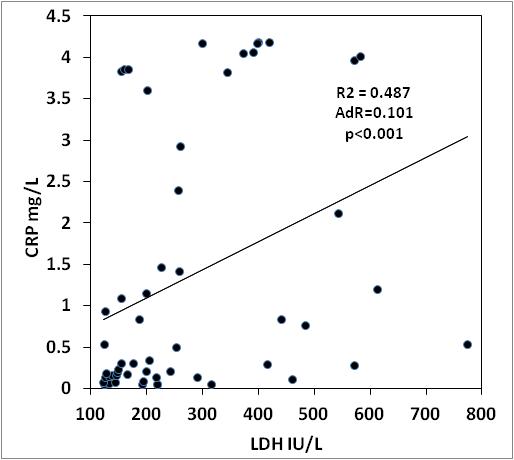
(a)



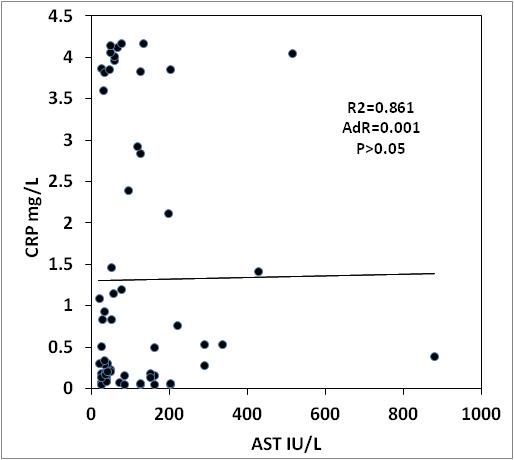
(b)



(c)



(d)

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**DISCUSSION**

In the present study we observed significant correlation among cardiac biomarkers and hsCRP levels which emphasize the importance of determination of hsCRP along with the other markers of myocardial damage. This observational study reports that the inflammatory markers measurement in ACS, prior to the tissue necrosis, is significantly related with classical cardiac enzyme markers and may be of prognostic significance. CRP has been studied mostly in acute coronary syndromes as a marker of proinflammatory state and plaque instability. In one study, HDL-C and CRP were reported to be independently associated with the prevalence of CAD [13]. Inflammation may play an important role in the pathogenesis of UA, and the plasma levels of CRP might have a higher prognostic value than the severity of coronary stenosis correlated with the clinical outcome of instability despite of lipid profile status [14] . In a large consecutive cohort of non-ST elevation ACS patients, CRP, an inflammatory marker, does not predict either the extension or the complexity of coronary disease. Even though CRP is a strong predictor of worse clinical outcome in patients with ACS, this could not be explained by the angiographic anatomic findings [15] . There was no significant correlation between hsCRP levels and Gensini score index. We conclude that there is no relationship between hsCRP levels and the presence and severity of CAD in patients with stable angina [16]. In patients with CSA, independently of revascularization, extension score and CRP levels predict cardiac adverse events, regardless of the presence or absence of flow limiting coronary lesions. Multivariate analysis showed extension score, revascularization and CRP levels, but not vessel score, to be independent predictors of the combined end-point [17]. Despite there is controversy regarding the variability of CRP levels [18,19,20]. In a recent study Kavsak et al indicated that high CRP concentrations, independent of the subjects' age, gender, and cTnI concentrations greater than 0.01 g/L predict long-term heart failure and death [21]. Our results opposes Morrow DA. et al, 1998 findings who reported that hsCRP levels rise in parallel to the amount of muscle necrosis, peaking at around day 2 post myocardial infarction (MI) and then falling [22]. However, he reported that persistent elevations of hsCRP 14 days after MI, was suggesting ongoing inflammation, and can predict recurrent events. Acute phase levels of CRP prior to marked elevations of cardiac troponin I (cTnI) may prime the body to respond to any necrotic or injured tissue. This theory finds support by De Servi et al. [23] who suggest that in ACS populations there is a large variability in CRP concentrations, yet those with high CRP at baseline are perhaps more hyper-responsive to stimuli, including circulating cTnI. A large number of basic science reports have suggested that circulating levels of C-reactive protein (CRP) are linked to prognosis in patients with atherosclerotic disease, heart failure, atrial fibrillation and myocarditis [24]. These data suggest that inflammatory processes play an independent role in the pathogenesis of myocardial infarction. A possible limitation of our study is small number of subjects. Long term prospective trials are needed at large scale to determine the true predictive value of inflammatory markers.

**CONCLUSIONS**

We conclude that hsCRP levels is a significant predictor of standard markers for myocardial damage and it may be a useful prognostic marker in acute coronary syndromes.

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**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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