**ORIGINAL ARTICLE**

# Serial Evaluation and Interelationship of C- Reactive Protein and Cardiac Enzymes Pattern in patients of Ischemic Heart Disease Undergoing Coronary Artery Bypass Surgery

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## ABSTRACT

**Background:** Coronary artery disease (CAD) is one of the leading causes of deaths in Pakistan. The relationship of CRP (C-reactive protein) with the mechanism of CAD involves a slow progression of atherosclerosis in the coronary arteries followed by myocardial necrosis. CRP has been considered as a vital bio-marker of inflammation. Elevation of high-sensitivity CRPis associated with grave prognosis in patients suffering from CAD.
**Aim:** To assess the serial measurement of plasma CRP levels and cardiac enzymes in adult patients of both sexes known to have CAD undergoing coronary artery bypass graft surgery (CABG), and correlate the findings.
**Methods:** The study involved a total of 60 adult people, 30 of them were diagnosed cases of CAD, scheduled for CABG (n=30), while other 30 were healthy control subjects (n=30). Blood samples equal to 5 ml were collected after written consent and serum was obtained from the obtained samples. Serial estimations cardiac enzymes and CRP levels were performed in both cases and control subjects, by using immuno-turbidometric assays.
**Results:** Plasma levels of CRP were significantly higher in patients of CAD, compared with control subjects. The estimated marginal mean of CRP levels before the bypass graft surgeries was significantly higher. The levels were observed to decrease after 2nd, 3rd and 4th postop days, and levels were equal to normal after 5th postop day
**Conclusion:** Average plasma levels of CRP in patients of CAD were approximately 7 mg/dl, but after the CABG surgery, plasma CRP levels decreased significantly till 4th post-operative day. There was no association between the CRP levels with the plasma levels of cardiac enzymes CK-Mb (Creatine Kinase MB fraction), AST (Aspartate Transaminase) and LDH (Lactate Dehydrogenase) on the 4th-post-operative day
**Keywords:** C-Reactive Proteins, Coronary Artery Bypass Graft, Coronary Artery Disease

## INTRODUCTION

CRP (C-reactive protein) is synthesized by the liver, and serves as a useful inflammatory biomarker in a variety of autoimmune and inflammatory diseases. In addition, CRP is an important indicator of risk of atherosclerotic events such as myocardial infarction and stroke (Szmitko et al 2003). The detailed relationship of CRP with CAD was first highlighted in 1982, in which high plasma levels of CRP were reported in patients who had cardiovascular complications (DeBeer et al 1982). Many epidemiological investigations have revealed that cigarette smoking, hypertension, diabetes mellitus and hyperlipidemia are considered as major independent risk factor for ischemic heart disease such as angina and myocardial infarction. There is substantial lack of understanding on the pathogenesis of coronary artery disease, and this gap has led to extensive research on the role of non-traditional risk factors in the development of coronary artery disease (Umesh et al 2003). Among several inflammatory markers associated with cardiac disorders, high sensitive C-reactive protein (hs-CRP) is most significantly associated with post-operative cardiovascular complications. Coronary artery bypass graft surgery (CABG) is the commonest cardiac surgery which has a risk of post-operative complications compared to other surgical procedures practiced at hospitals. These increased post-operative levels of hs-CRP are significantly linked with unfavorable prognosis in

patients suffering from acute myocardial infarction (Toss H et al 2010). The plasma levels of CRP peaks after 15 hours following cardiac arrest, whereas, CRP levels peaked around 50 hours after the onset of cardiac pain, and by this time, CK-Mb levels are usually returned to normal (Lee TM et al., 2012). CRP levels observed in pre-operative patients in the range of 3 to 10 mg/dl and or over 10 mg/dl range spent a median of 8 days of hospitalization after CABG, compared with 7 days of post-operative days of hospitalization of patients with pre-operative CRP levels of 1 to 3 mg/dl. In the current study, it was confirmed that patients with circulating CRP levels greater than 10 mg/dl had worse prognosis after cardiac surgery, this finding was in accordance with similar work on patients of cardiac surgery (Perry ET 2010). It has been known that post-operative CRP levels can be of adverse outcomes in CABG patients. CRP levels ≥ 3 mg/dl indicates high risk of post-operative death. A comparison was documented between the outcomes in patients who showed increased inflammatory response 4 hours post-operative with patients who did not show this pattern of response (Chew DP 2013). Recently, it was documented that patients with increased levels of CRP suffering from unstable angina exhibited significant myocardial injury as compared to patients of unstable angina with normal CRP levels (Toss H et al 1997). This study has highlighted CRP as a significant marker of generalized inflammation, and its active role in progression of atherogenesis and disruption of atheromatous plaque, thus serving as a useful risk factor in a variety of inflammatory clinical settings. CRP appears to

serve as an independent marker of atherosclerosis especially in the presence of risk factors such as smoking, hypertension and diabetes mellitus in selected Pakistani population. The serum levels of CRP are likely to alter the pattern of patient's management, lines of treatment and monitoring of patient's response to treatment. The objective of the present study was to assess the serial measurement of cardiac enzymes and CRP levels in adult patients of both sexes known to have coronary artery disease, undergoing bypass graft surgery (CABG) and subsequent correlation of evaluated variables.

## PATIENTS AND METHODS

Present study was conducted in the cardiology unit of Doctor's Hospital Lahore, in collaboration with Chughtai's Laboratory, for the evaluation of CRP levels and cardiac enzymes estimation on automation. The study included a total of 60 individuals, among which 30 individuals were diagnosed cases of coronary artery disease scheduled to undergo coronary artery bypass graft surgery (CABG). Remaining 30 individuals were healthy adults considered as controls. These control subjects were evaluated on clinical history, angiograms and ECG tests to exclude any underlying cardiac abnormality. In these two groups, both males and females were included with ages ranging between 45 to 75 years. There were 42 male and 18 female subjects among the cases. Among the control subjects, there were 20 male and 10 female subjects. Mean age of the patients was 57.20±8.57 years, and mean age of healthy control subjects was 56.9±7.27 years.

**Sample collection:** After obtaining consent from patients, 5 ml of venous blood was collected from the ante-cubital vein of forearm, serum was extracted and analysis of cardiac enzymes and CRP was performed. CRP analysis was performed by immune-turbidometric method, and final measurements were made at 340 nm. Serum ASR levels were estimated by using spectrophotometric method, and absorbance was read at 280 nm after one, two and three minutes intervals. CK-MB fraction was estimated by spectrophotometric method and absorbance read at 340 nm. Lactate Dehydrogenase enzyme levels were estimated by employing kinetic colorimetric method and final absorbance was read at 530 nm. The data was recorded by using SPSS version 22.0 and all quantitative measures were represented as mean±standard error. To evaluate mean difference between cases and controls, paired t-test was used. Pearson correlation was applied to evaluate inter-relationship between serum levels of CRP and cardiac enzymes.

## RESULTS

The mean age of the cases was 57.20 ± 8.57 and mean age of the controls was 56.9±7.27 years and there was no significant difference in the mean age of patients and controls. Serum CRP levels were observed to be significantly higher in cases, compared with healthy controls (<0.001).

CRP level of control subjects was statistically significantly lower than the cases (<0.001). It was noted that the plasma levels of CRP decreased on 1st 2nd and 4th postoperative days after the CABG operation. However, on the 4th and 5th post-operative days the plasma levels of CRP were observed to be equal to that of healthy controls. This decline in plasma CRP levels decline till the 4th postoperative day was probably due to decrease in the inflammation. Plasma Creatine kinase levels were raised at the time of CABG procedure and decreased gradually after 3rd post-operative day. After that it again showed a slight increase in plasma levels, which may be due to ischemic insult during the CABG surgery. Similarly, AST levels were significantly high on the 3rd postoperative day, compared with the base line levels prior to CABG surgery. After 3rd post-operative day, its plasma levels declined gradually. This transient rise in plasma levels of AST may be due to hemolysis commonly seen in post CABG surgical patients. LDH levels at baseline and at 1st post-operative day were significantly different. The slight decrease in plasma levels on 3rd post-operative day was probably attributed to hemodilution present in these patients after the CABG surgery. Correlation between CRP levels and the cardiac enzymes was established, based on the observations of this study. CRP was significantly correlated with AST and LDH (r =0.962 and p-value of 0.000). AST was also significantly correlated with LDH (r = 0.888 and p-value= 0.000). In all control individuals, CRP was below 3.0 mg/ l, whereas, in cases, only 7 (11.67 %) patients CRP level was ≤ 3.0

Students t test 7.120

|  | Mean | Std. Deviation | Std. Error Mean |
|---|---|---|---|
| C.R.P (Control) | 0.763 | .3189 | 0.0412 |
| C.R.P(Cases) | 7.88 | 3.503 | 0.452 |

P value<0.001

Table 1: Comparison of CRP levels at specific intervals

|  |  | C.R.P1 | C.R.P2 | C.R.P3 | C.R.P4 | C.R.P5 |
|---|---|---|---|---|---|---|
| C.R.P | Pearson Correlation | 0.977** | 0.965** | 0.952 | 0.745** | 0.932** |
|  | Sig. (2-tailed) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
|  | N | 60 | 60 | 60 | 60 | 60 |
| C.R.P1 | Pearson Correlation |  | 0.974** | 0.964** | 0.626** | 0.928** |
|  | Sig. (2-tailed) |  | <0.001 | <0.001 | <0.001 | <0.001 |
|  | N |  | 60 | 60 | 60 | 60 |
| C.R.P2 | Pearson Correlation |  |  | 0.977** | 0.655** | 0.948** |
|  | Sig. (2-tailed) |  |  | <0.001 | <0.001 | <0.001 |
|  | N |  |  | 60 | 60 | 60 |
| C.R.P3 | Pearson Correlation |  |  |  | 0.638** | 0.955** |
|  | Sig. (2-tailed) |  |  |  | <0.001 | <0.001 |
|  | N |  |  |  | 60 | 60 |
| C.R.P4 | Pearson Correlation |  |  |  |  | 0.596** |
|  | Sig. (2-tailed) |  |  |  |  | <0.001 |
|  | N |  |  |  |  | 60 |

Table II:

| | | Mean | Std. Deviation | Std. Error Mean | p-value |
|---|---|---|---|---|---|
| Pair 1 | C.R.P | 7.87 | 3.503 | 0.452 | <0.001 |
| | C.R.P1 | 7.47 | 3.427 | 0.442 | |
| Pair 2 | C.R.P1 | 7.47 | 3.427 | 0.442 | 0.026 |
| | C.R.P2 | 7.23 | 3.228 | 0.417 | |
| Pair 3 | C.R.P2 | 7.23 | 3.228 | 0.417 | 0.002 |
| | C.R.P3 | 6.95 | 3.254 | 0.420 | |
| Pair 4 | C.R.P3 | 6.95 | 3.254 | 0.420 | 0.025 |
| | C.R.P4 | 6.15 | 3.063 | 0.395 | |
| Pair 5 | C.R.P4 | 6.15 | 3.063 | 0.395 | 0.708 |
| | C.R.P5 | 6.28 | 3.048 | 0.394 | |

Table III : Correlation of CRP levels in the 5 postoperative days after CABG

| | | Mean | Std. Deviation | Std. Error Mean | p-value |
|---|---|---|---|---|---|
| Pair 1 | CK-MB | 20.33 | 28.007 | 3.616 | 0.439 |
| | CK-MB1 | 19.78 | 27.211 | 3.513 | |
| Pair 2 | CK-MB1 | 19.78 | 27.211 | 3.513 | 0.636 |
| | CK-MB2 | 18.18 | 6.680 | 0.862 | |
| Pair 3 | CK-MB2 | 18.18 | 6.680 | 0.862 | 0.007 |
| | CK-MB3 | 18.65 | 25.893 | 3.343 | |
| Pair 4 | CK-MB3 | 18.65 | 25.893 | 3.343 | 0.442 |
| | CK-MB4 | 19.12 | 24.293 | 3.136 | |

Table IV: CK-MB Levels

| | | Mean | Std. Deviation | Std. Error Mean | p-value |
|---|---|---|---|---|---|
| Pair 1 | A.S.T | 38.77 | 58.843 | 7.597 | <0.001 |
| | A.S.T1 | 23.28 | 40.295 | 5.202 | |
| Pair 2 | A.S.T1 | 23.28 | 40.295 | 5.202 | 0.046 |
| | A.S.T2 | 25.10 | 43.766 | 5.650 | |
| Pair 3 | A.S.T2 | 25.10 | 43.766 | 5.650 | <0.001 |
| | A.S.T3 | 132.92 | 189.653 | 24.484 | |
| Pair 4 | A.S.T3 | 132.92 | 189.653 | 24.484 | <0.001 |
| | A.S.T4 | 31.22 | 51.081 | 6.595 | |

Table V : Showing association of AST levels with each other .

| | | Mean | Std. Deviation | Std. Error Mean | p-value |
|---|---|---|---|---|---|
| Pair 1 | L.D.H | 390.97 | 248.177 | 32.040 | <0.001 |
| | L.D.H1 | 429.92 | 263.607 | 34.031 | |
| Pair 2 | L.D.H1 | 429.92 | 263.607 | 34.031 | 0.010 |
| | L.D.H2 | 446.65 | 262.064 | 33.832 | |
| Pair 3 | L.D.H2 | 446.65 | 262.064 | 33.832 | 0.311 |
| | L.D.H3 | 433.53 | 273.145 | 35.263 | |
| Pair 4 | L.D.H3 | 433.53 | 273.145 | 35.263 | 0.473 |
| | L.D.H4 | 444.97 | 268.778 | 34.699 | |

Table VI: Correlation table: Ck-MB cardiac enzyme in patients of coronary artery disease

| | CK-MB1 | | CK-MB2 | CK-MB3 | CK-MB4 | |
|---|---|---|---|---|---|---|
| | 0.981** | 0.976** | 0.972** | 0.972** | | |
| | <0.001 | <0.001 | <0.001 | <0.001 | | |
| | 60 | 60 | 60 | 60 | | |
| CK-MB1 | Pearson Correlation | | | 0.984** | 0.975** | 0.981** |
| | Sig. (2-tailed) | | | <0.001 | <0.001 | <0.001 |
| | N | | | 60 | 60 | 60 |
| CK-MB2 | Pearson Correlation | | | | 0.991** | 0.995** |
| | Sig. (2-tailed) | | | | <0.001 | <0.001 |
| | N | | | | 60 | 60 |
| CK-MB3 | Pearson Correlation | | | | | 0.985** |
| | Sig. (2-tailed) | | | | | <0.001 |
| | N | | | | | 60 |

**Correlation between CPR and other Cardiac Bio Markers**

Table VII: Correlation of cardiac markers

| | | CK-MB | A.S.T | L.D.H |
|---|---|---|---|---|
| C.R.P | Pearson Correlation | .081 | .084 | .165 |
| | Sig. (2-tailed) | .541 | .521 | .207 |
| | N | 60 | 60 | 60 |
| CK-MB | Pearson Correlation | | .962** | .897** |
| | Sig. (2-tailed) | | .000 | .000 |
| | N | | 60 | 60 |
| A.S.T | Pearson Correlation | | | .888** |
| | Sig. (2-tailed) | | | .000 |
| | N | | | 60 |

**Means of CRP (pre-op) and five Post -op levels**
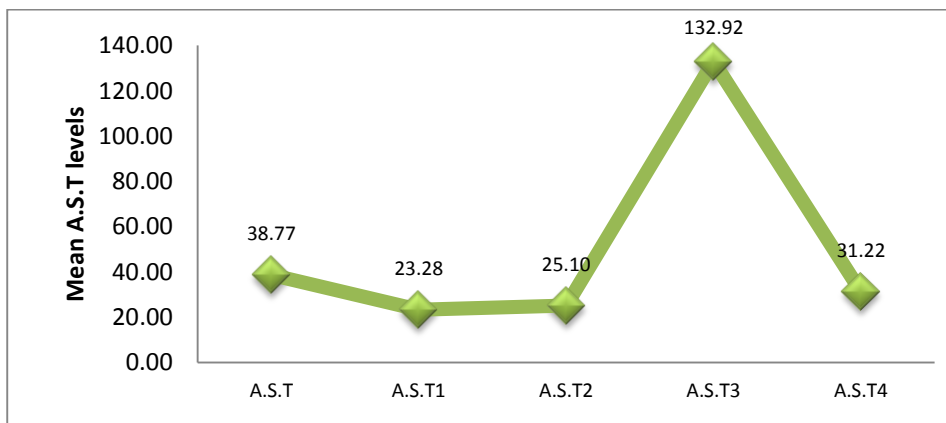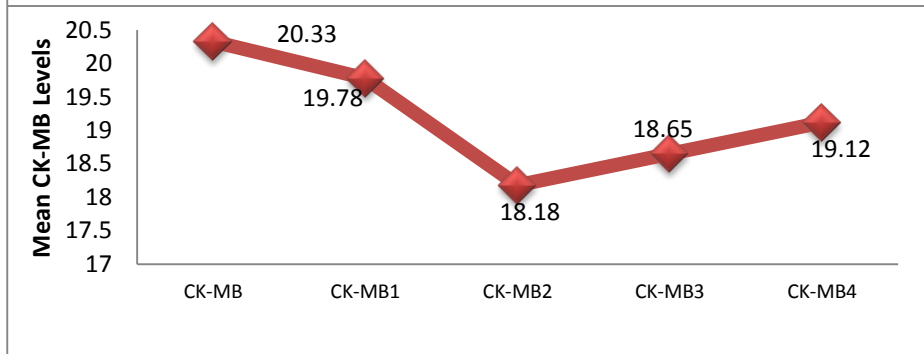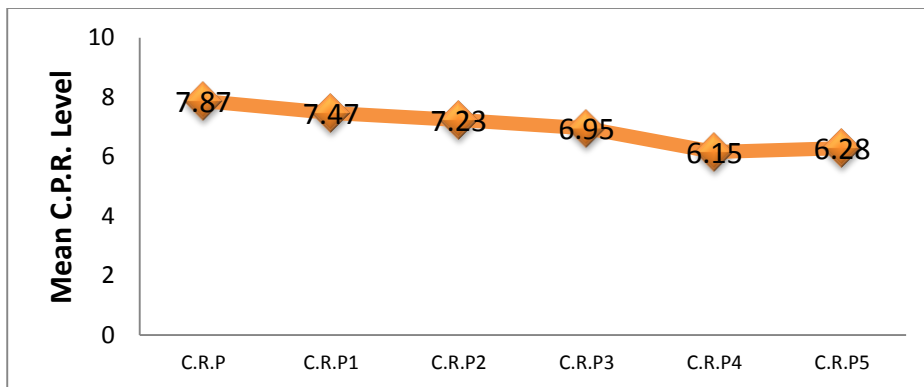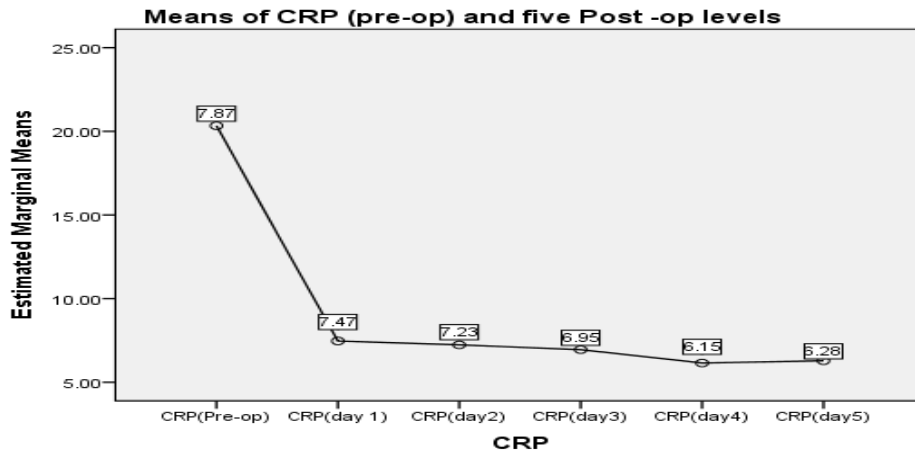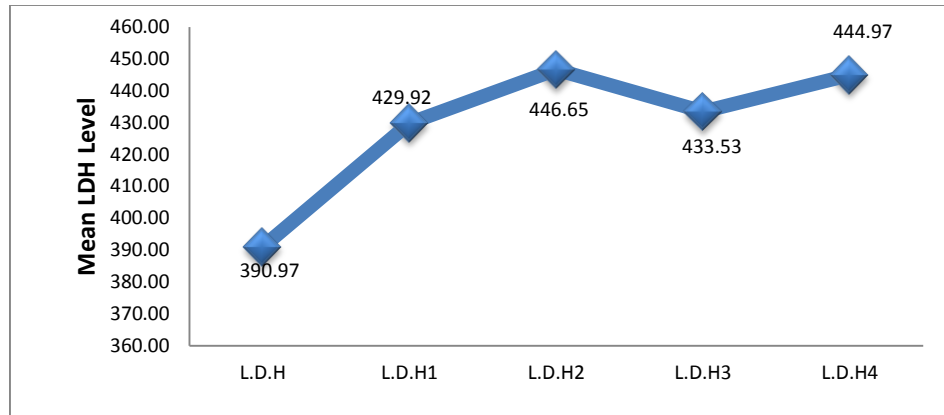
## DISCUSSION

CRP concentration rise in blood during acute infections or clinical states causing extensive tissue damage (Kaptoge et al., 2010). According to American Heart Association (AHA), plasma levels of CPR are clinically categorized into two fundamental groups; ≤3 mg/dl and >3 mg/dl. At the base line interval, plasma levels of CRP more than 3 has been considered as an independent risk factor for the development of heart disease (Danesh et al., 1998). In the present study, the average plasma levels of CPR level was 7mg/l in patients with myocardial infarction. After bypass surgery, the CPR levels gradually decreased and was statistically significantly till 4th post-operative day. However, on 5th post-operative day the CRP levels raised were slightly raised, but the difference was not statistically significant. The raised plasma levels of CPR were probably attributed to high CPR levels at the time of base line and prior to bypass surgery. In addition, creatine kinase levels were found to be elevated at the time of base line, prior to bypass surgery, then plasma levels of creatine kinase gradually decreased till 3rd post-operative day, and interestingly its plasma levels were again observed to increase. CK-MB levels were, however, found to be lowest on 3rd post-operative day. After bypass surgery, the raised plasma levels of CK-MB level indicated the ischemic insult during the bypass surgery (Kwinecki et al., 2003).

## CONCLUSION

The aim of the present study is to investigate the plasma hs-CRP and cardiac enzymes levels before and after CABG surgery of patients suffering from coronary artery disease. The inter-relationship is statistically established between these cardiac enzymes. It is observed that mean hs-CRP level was 7mg/l in patients of myocardial infarction before the bypass surgery. These high plasma CRP levels are probably due to progressive inflammatory processes in coronary artery atherosclerosis. After CABG surgery, plasma hs-CRP levels gradually declines till the 4th postoperative day, which is probably attributed to decrease inflammatory processes after the bypass surgery. These cardiac markers are of less significance in long term post-operative management of patients of coronary artery disease after the bypass surgery.

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