High Sensitive C-Reactive Protein Levels in Patients with Acute Coronary Syndrome

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ABSTRACT:

BACKGROUND:

Patients with ischemic discomfort may present with or without STsegment elevation on the ECG. The majority of patients with ST-segment elevation ultimately develop a Q-wave AMI (QMI). Patients who present without ST-segment elevation are either experiencing unstable angina (UA) or a non-STsegment elevation MI (NSTEMI). Most patients with NSTEMI do not evolve a Q-wave and are subsequently referred to as having sustained a non-Q-wave MI (NQMI). The spectrum of clinical conditions ranging from acute myocardial infarction through minimal myocardial injury to unstable angina comprises the acute coronary syndrome (ACS). Measurement of C-reactive protein (CRP) may have practical clinical significance in the management of patients hospitalized for suspected ACS.

OBJECTIVE:

To study different follow up measurements of high sensitive C-Reactive Protein (hsCRP) levels in ACS patients and to compare the difference between (NSTEMI) and (STEMI) patients.

METHODS:

122 patients with ACS participate in this study through years 2006-2008. Three serial hsCRP levels at baseline on admission to hospital before 12 hours of symptom onset, peak levels at 3 days and follow up levels after 5 days were analyzed and compared between non-ST elevation AMI, ST elevation AMI and UA elevation.

RESULTS:

The results were compared with those of healthy groups as controls.

The results showed a significant elevation in serum CRP levels on 1st, 3rd and 5th reaching optimum value on day 3 post infarction in QMI and NQMI patients, While there was a non significant increase in serum CRP level in patients with UA on day 1, and day 3 post attack.

CONCLUSION:

STEMI patients have significantly higher peak CRP levels compared to NSTEMI patients. These data suggest that inflammatory processes play an independent role in the pathogenesis of myocardial infarction. Thus, CRP assessment may assist in risk stratification after myocardial infarction.

KEY WORD:C-reactive protein; myocardial infarction; unstable angina; acute coronary syndrome.

INTRODUCTION:

CRP the classical acute-phase protein, which is an exquisitely sensitive systemic marker of disease with broad clinical utility for monitoring and differential diagnosis [(1)].

CRP was originally named for its ability to bind the C-polysaccharide of Pneumococcus. It acts as an opsonin for bacteria, parasites and immune complexes, and can activate the classical pathway of complement [(2)]. CRP is a useful marker of inflammation in patients with IHD, particularly unstable angina and AMI [(3)]. Inflammation is a critical factor in the pathophysiology of atherosclerosis and its thrombotic complications [(4,5)]. Increased levels of inflammatory markers predict adverse events in different manifestations of coronary atherosclerotic disease [(6,7)].

During recent years there has been a growing recognition that inflammation plays an important role in the development of cardiovascular diseases [(8, 9, 10, and 11)]. Inflammatory mechanisms play a pivotal role in the atherosclerotic process and a growing body of experimental evidences suggests that inflammation is involved in the

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pathogenesis of ACS and influences their clinical evolution [12].

In fact, in patients with ACS, coronary atherosclerotic plaques are characterized by an abundant inflammatory infiltrate. Among several markers of systemic inflammation, CRP shows the strongest associations with vascular events, and the addition of CRP to total cholesterol dramatically improves risk predication [13]. Accumulating evidence has also established the role of inflammatory biomarkers in the prognosis of patients with ACS. Interest has primarily focused on (CRP), a biomarker that independently predicts future vascular events [14]. An increasing number of studies suggest that CRP progression in healthy individuals and in the ACS [15]. In apparently healthy individuals, a raised CRP value indicates an increased risk of developing atherosclerotic vascular disease [16].

It has been suggested that CRP is produced and released within the coronary circulation of patients with ACS; this is associated with impairment of endothelial function, suggesting a new pathophysiological link between CRP and ACS[17]. There is growing evidence of the prognostic importance of CRP in unstable angina; it has been shown to be increased in patients with unstable angina. Elevated CRP levels are associated with an increased risk of subsequent cardiovascular event in unstable angina [18]. Recent data demonstrate that CRP is a strong independent predictor of adverse cardiac events and death in patient with ACS. But also in patients with stable IHD and in apparently healthy men and women. Moreover, even among patients with troponin-negative ACS, elevated levels of CRP are predictive of future risk [19]. Patients with elevated concentration of serum CRP admitted to the hospital because of AMI are at an increased risk of dying [20].The majority of authors concur in that the admission CRP value reflects the baseline inflammatory status of the patient; thus, patients with ACS and high CRP levels at admission usually experience more cardiovascular complications during follow-up [21].

PATIENTS AND METHOD:

This study was concluded on patients admitted to the CCU in AL-Kadhmia teaching hospital during the period from April 2006 to 2008. It comprise of 122 patients with ACS (42 UA and 80 AMI), nine died and thirty-one were excluded from the study of these 8 had previous HX of IHD and twenty three had other disease that may effect the parameter to be diagnosed, particularly patients with infections, malignancies, rheumatoid arthritis, trauma, nephritic syndrome, chronic active hepatitis, biliary cirrhosis, diabetes, alcohol-induced liver cirrhosis.

Patients with AMI meet at least two of the inclusion WHO criteria of the study: a history of chest pain, evolutionary changes on the ECG, and elevation of serial cardiac enzymes. The patients diagnosed by cardiologist depending on the result of clinical examination, ECG, echo, CXR, lipid profile, and cardiac enzyme.

1- Group:

57 patients with AMI (32 males and 25 females). These patients were subdivided as following:

A- 42 patients with QMI (23 male and 19 female).

B- 15 patients with NQMI (9 males and 6 females)

2-Group 2:

35 patients suffered from unstable angina (20 males and 15 females).

3- Group 3:

The control subjects were volunteers (13 males and 9 females) who had no evidence of CHD.

The characteristic of these patients are present in the following table:

Table (*): Age and sex of the studied groups

Groups	Total	Male	Female	Age Range
Control	22	13	9	27-55
AMI	57	32	25	40-70
QMI	42	23	19	45-67
NQMI	15	9	6	42-60
Unstable Angina	35	20	15	35-55

METHOD:

Three milliliters of venous blood were withdrawn from each patient. Samples were transferred into clean new plane tube, left at room temperature for 15 minutes for clotting, centrifuged, and the separated serum was used for measurement of hsCRP. The samples was stored at –20^{o} C until analysis, which was done within one month after collection.

Serum hs-CRP was measured using ELISA kit DRG CRP, HS (C-Reactive Protein) (EIA-3954).

hs-CRP Ranges

Ranges of hs-CRP in prediction of risk for cardiovascular disease (CVD) are:

- <1.0 mg/L Low CVD risk
- 1.0-3.0 mg/L Average risk for CVD
- >3.0 mg/L High risk for future CVD

If results are >10.0 mg/L, the patient should be evaluated for an acute inflammatory condition.

STATISTICAL ANALYSIS

All the recorded parameters were calculated and presented as means and standard deviation of the mean. The statistical differences obtained during the research were calculated using the (students t-test) to compare the different groups of patients. Value were considered significant when p <0.05.

RESULTS:

The results of serum hsCRP in control, QMI, NQMI, and UA patients are shown in figures & tables (I), (II), and (III) respectively

A highly significant increase (p<0.0001) in serum hsCRP concentration was found on day 1, day 3, and day 5 post infraction in QMI patients. Also a high significant increase (P<0.0001) was observed on day 1, day 3, and day 5 after the infarction in NQMI patients.

There was a non significant increase (P>0.05) in serum hsCRP level in patients with UA as compared with control group.

The results of serum hsCRP in control, QMI, NQMI, and UA patients are shown in figures & tables (I), (II), and (III) respectively.

Table (I): The mean (±SD) values of serum hsCRP levels (mg/L) in Control and QMI Patients.

	Control	QMI-D1	QMI-D3	QMI-D5
No. of healthy & QMI patients	22	41	41	16
Mean	6	24.1	66.7	50.8
± SD	3.2	4.9	7	8.1
p-value	-	< 0.0001	< 0.0001	< 0.0001

Table (II): The mean (±SD) values of serum hsCRP levels (mg/L) in Control and NQMI Patients.

	Control	NQMI-D1	NQMI-D3	NQMI-D5
No. of healthy & NQMI patients	22	15	15	8
Mean	6	17.5	54.1	36.7
± SD	3.2	9	8.4	9.4
p-value	-	< 0.0001	< 0.0001	< 0.0001

Table (III): The mean (±SD) value of serum hsCRP (mg/L) levels in Control and Unstable Angina Patients.

	Control	UA-D1	UA-D3	UA-D5
No. of healthy & UA patients	22	35	35	7
Mean	6	10.4	13.7	9
±SD	3.2	3	3.4	2.3
p-value	-	NS	NS	NS

DISCUSSION:

CRP, an acute-phase reactant produced in Liver, is none-specific marker of acute inflammation disease, infections and neoplastic disease. Following an AMI, fibrinogen, CRP, and IL-6 levels are reported to be significantly higher in patients with complications, both as in-hospital and follow-up prognostic indicators [6]. CRP data indicated an increase in the concentration in patients with ACS during 12 hr period of hospital admission which is in agreement with Auer et al (2002) [22], Iltumur et al (2005) [23]. In patients with ischemic chest pain, a raised CRP value on hospital admission is associated with an adverse prognosis [16]. CRP may even be a link between systemic and local inflammatory processes, because it has been shown to be systemically elevated in patients with unstable angina, and most recently has been shown to be involved in the initiation and progression of early atherosclerotic lesion [24]. CRP has been shown to posses some proatherogenic properties that may influence the progression of atherosclerosis [25].

Pepys & Hirschfield 2001[26] suggested a direct role for CRP in the pathogenesis of atherosclerosis and post-myocardial infarction inflammation. C-reactive protein, present in atherosclerotic plaques, binds to oxidized LDL and enhances of the ability of macrophages to phagocytosize LDL and form foam cells through the CRP receptor CD32. Furthermore, the presence of CRP within most atherosclerotic plaques and all AMI lesions, coupled with binding of CRP to Lipoproteins, and its capacity for pro-inflammatory complement activation, suggests that CRP may contribute to the pathogenesis and complications of CVD [1,27].

Blake & Ridker 2001[19] suggeded that the CRP concentration might reflect the vulnerability of the atheromatous lesion and the likelihood of a plaque to rupture. It has been reported that CRP correlates with the number of vulnerable atherosclerotic plaques with superficial foam cells, large necrotic cores and thin fibrous cap atheroma [28]. These finding indicate that serum CRP levels are a marker of CAD activity and may be a biochemical marker of the diffuse inflammatory process that leads to multifocal plaque instability. Moreover, it has been suggested that CRP may not only be a marker of generalized inflammation but directly participates in both atherogenesis and athermatous plaque disruption ([29, 30].

CRP facilitates native LDL uptake into macrophages [31]; promotes monocyte activation [32]; and a procoagulant effect by inducing monocytes to synthesize tissue factor. [33]; activate the classic pathway of complement activation [34]; and has been demonstrated to colocalize with terminal complement complexes in established coronary plaques [35].

The findings of Sánchez et al 2006 [36] can also help interpret the mechanisms that lead to increased CRP in ACS. In short, it seems that 3 mechanisms are implicated:

1. Rupture of unstable plaque or high presence of unstable plaque in patients with ACS could trigger an inflammatory response and, as a result, release of CRP as an acute-phase mediator [37]. It has even been suggested that CRP could exert direct effects on the arterial wall and trigger destabilization [38].
2. From the finding of Bodi et al 2003 [39], the principle mechanism responsible for CRP elevation ACS is clearly necrosis. Levels are much lower in non-ST-elevation infarction ACS which has less myocardial damage. In patients with unstable angina, levels are even lower.
3. Inflammatory response varies greatly from individual to individual. Recently de Servi et al (2005) [40] have suggested that CRP elevation during ACS is partly determined by baseline CRP levels and, therefore, by the baseline inflammatory status. The higher the CRP levels before ACS, the larger the increase during the acute episode. Thus, a greater increase in this marker during ACS would also indicate that the arterial system is more inflamed, with a larger number of unstable plaques and, in short, a higher baseline cardiovascular risk.

Sanchis et al 2004 [37] suggested that rupture of unstable plaque or high presence of unstable plaque in patients with ACS could trigger an inflammatory response and, as a result, release of CRP as an acute-phase mediator.

Reza, 2012 [41] assessed the relationship between plasma high sensitivity C-reactive protein level with severity of ACS. Vahdat et al., 2007 [42] found that elevated Hs-CRP was significantly correlated with electrocardiogram defined coronary artery disease. A significant difference has been observed in present study regarding the value of hs-CRP in CHD subjects as compared to

normal healthy control subjects which reveals that there is an association between hs-CRP and CHD. These results are in accordance with Pasupathi et al 2009 [43]. The present study showed that a peak CRP concentration were significantly lower in UA group than in the AMI and NQMI groups which is in agreement with Iltmur et al 2005 [23]. On the other hand, the present data reported that patients with STEMI have significantly higher peak CRP levels compared to patients with NSTEMI. These data suggest that inflammatory processes play an independent role in the pathogenesis of myocardial infarction. These findings were compatible with those recently reported by syed et al 2011 [44]. The higher increase in CRP levels during Q-wave MI than in non Q-wave MI seems to be linked to the extension of myocardial damage, rather than to the pre-existing inflammation [45].

CONCLUSION:

1-This study indicates that serum C- reactive protein could be a cardiovascular risk factor, with elevated level associated with the development of the disease.

2-The role of C-reactive protein in the pathogenesis of atherosclerosis reflects its usefulness as a predictor of cardiovascular events

3- Serum hs-CRP levels show significant correlation with the severity of ACS as assessed by Elisa method.

4- Peak CRP levels are significantly higher in QMI patients, when compared to NQM patients. This confirms that ACS is associated with systemic evidence of inflammation.

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