ORIGINAL RESEARCH ARTICLE

High-sensitive C-reactive Protein and Lipid Profile in Early Phase of Acute Coronary Syndrome

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Abstract

Aim and objective: The goal of this study was to examine the association of high-sensitive C-reactive protein (hs-CRP) and lipid profile within 24 hours of onset of symptoms in acute coronary syndrome (ACS) patients.

Materials and methods: We studied 300 patients with ACS and 100 age- and sex-matched control subjects with no cardiac disease. Acute coronary syndrome patients were classified into two groups (I) onset of ACS symptoms <6 hours and (II) onset of ACS symptoms ≥6 and <24 h. Blood samples were obtained within 24 hours of hospital admission. High-sensitive C-reactive protein and lipid profile were analyzed by latex enhanced immunoturbidimetric method and enzymatic colorimetric methods, respectively.

Results: Overall serum levels of hs-CRP at the early phase of ACS were significantly higher (9.15 ± 5.89 *vs* 1.08 ± 0.7 mg/L, $p < 0.001$), along with altered lipid profile in patients than in control subjects. In subgroup analysis, serum concentrations of hs-CRP were approximately 3-fold higher in group I when compared with the control group (3.4 ± 2.08 *vs* 1.08 ± 0.7 mg/L, $p < 0.001$), and the levels of hs-CRP were almost 12-fold higher in group II than the controls (12.98 ± 4.26 *vs* 1.08 ± 0.7, $p < 0.001$). Between ACS patients subgroups, serum hs-CRP levels were almost 4-fold higher in group II when compared with group I ($p < 0.001$).

Conclusions: Our results demonstrate that hs-CRP is significantly higher in the patient's group during the early phase of ACS suggesting that inflammatory processes play a role in ACS.

Keywords: Acute coronary syndrome, Coronary heart disease, C-reactive protein, Dyslipidemia, Lipid profile.

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Introduction

Coronary heart disease (CHD) is one of the leading causes of mortality and morbidity all over the world, including India. It is now generally accepted that inflammation and inflammatory processes contribute significantly in different stages in the pathogenesis of CHD, including the lifelong process of atherogenesis, the acute atherothrombotic event, which causes ischemic necrosis in acute myocardial infarction (AMI) and the myocardial damage following ischemia.[1] In consideration of the important role that inflammatory processes play in determining plaque stability, recent work has focused on whether biomarkers of inflammation may help to improve risk stratification and identify patient groups who might benefit from particular treatment strategies. Among them, C-reactive protein (CRP), a prototype marker of the inflammatory process, is the most studied both as a causal factor and in the prediction of CHD.[2] C-reactive protein is a pentamer, produced in the liver in response to interleukin (IL)-6 which is stimulated, in turn, by tumor necrosis factor-α and IL-1.[3]

Several population-based prospective studies of CHD have reported a close association of subtle, prolonged increases in baseline high-sensitive C-reactive protein (hs-CRP) levels with CHD risk.[1] These findings have been consistent in different populations with diverse ethnic backgrounds and in diverse clinical settings, and have predicted the risk of various cardiovascular outcomes, including incident AMI, stroke, sudden cardiac death, peripheral artery disease, and also incident diabetes and new-onset hypertension.[4,5] High-sensitive C-reactive protein levels within 6 hours of onset of the acute coronary syndrome (ACS), before they can be affected by myocardial damage, reflect the baseline levels of serum hs-CRP in these patients. The majority of authors concur that the admission hs-CRP value reflects the baseline inflammatory status of the patient; thus, patients with ACS and high hs-CRP levels at admission usually experience more cardiovascular complications during follow-up.[6]

Dyslipidemia is recognized as one of the major risk factors for CHD. The role of lipids in the development and progression of atherosclerosis is well established, and low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) have been associated with CHD risk consistently in multiple clinical investigations.[7] Accumulation and modification of LDL-C in the arterial intima initiates the inflammatory cascade resulting in plaque formation. Although current guidelines recommend measurement of serum lipids after admission for patients with an ACS, less than one-half of these patients have serum lipids measured within 24 hours of admission. This is of importance because in-hospital lipid testing and initiation of statin use in patients with an ACS are strongly associated with their use on discharge.[8] Therefore, in the present study, we have estimated the levels of inflammatory marker hs-CRP

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along with lipid profile within 24 hours of onset of symptoms of ACS, to evaluate the changes in these markers in the early phase of ACS.

Materials and Methods

Patients

The present study was carried out on 300 ACS patients and 100 controls. All the patients were selected from the coronary care unit, heart command center, and cardiology department of a tertiary care hospital in Gurgaon, India. We stratified all ACS patients into two groups[1] onset of ACS symptoms <6 hours and[2] onset of ACS symptoms ≥6 and <24 h. We included patients if they met all the following criteria: (a) all patients had ACS at baseline; (b) blood samples for hs-CRP determination were obtained within 24 hours from the onset of symptoms. MI was defined by detection of rise in cardiac biomarkers of necrosis (cTroponin I) with at least 1 value above the 99th percentile upper reference limit, together with evidence of myocardial ischemia with at least 1 of the following: electrocardiographic changes indicative of new ischemia (new ST-T changes or new left bundle branch block), new pathological Q waves in at least 2 contiguous leads, imaging evidence of new loss of viable myocardium, or new wall motion abnormality.[9] Unstable angina was defined as chest pain with electrographic changes and no biomarker of myocardial necrosis has been elevated.

Diabetes was defined as a previous diagnosis, use of anti-diabetic medicines, or a fasting venous blood glucose level ≥126 mg/dL on 2 occasions in previously untreated patients. Hypertension was defined as patient systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg at rest, over a series of repeated measurements, or on treatment with antihypertensive medications. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Individuals with rheumatic disease, chronic liver diseases, renal disorders, cancer, sepsis, and patient critically ill with <1-month duration infectious diseases and surgical procedure in 3-month duration and on statin therapy were excluded from the study. One hundred healthy controls, who were similar in age and gender to the ACS patients were also recruited from blood donors, hospital staff, and also from the health check-up individuals. Written consent was obtained from all study participants. All ethical measures were taken before starting the study.

Venous blood was drawn at admission to the coronary care unit of the hospital. Blood was allowed to clot at room temperature, and serum was obtained immediately by centrifugation at 3500 rpm for 10 min. Serum was aliquoted into plastic tubes and stored at −27°C until assayed. Serum levels of hs-CRP were determined by latex enhanced immunoturbidimetric assay. Lipid profile, comprising TC, triglycerides (TG), LDL-C, and high-density lipoprotein cholesterol (HDL-C) was analyzed by enzymatic colorimetric methods. All the required reagent kits were provided by the VITROS chemistry products and all parameters were assayed in VITROS 5600 automatic analyzer according to the instructions of the manufacturer.

Statistical analysis

All statistical analyses were made using Statistical Package for the Social Sciences 21 (SPSS 21). Baseline variables were summarized as mean (SD) for continuous variables and as number (percentage) for categorical variables. Independent sample *t*-tests were used to compare the mean values of variables between all ACS patients and controls, whereas the Chi-square test was used for the association between two categorical variables. Levels of three or more groups were compared by one-way analysis of variance (ANOVA) followed by Sidek's *post hoc* test. A probability value $p < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics of the entire study cohort are depicted in Table 1. Because of matching criteria, there were no differences in terms of age or gender. In the present study, each group comprised of almost 60% males, with 115 (38.3%) female and 185 (61.7%) male patients with ACS and 38 (38%) female and 62 (62%) male controls. The mean age of the ACS subjects and controls was 59.08 (±6.75) and 58.95 (±7.59) years, respectively. One hundred and twenty-five (41.7%) patients had hypertension, 77 (25.7%) had diabetes, 92 (30.7%) were smokers, and 88 (29.3%) were alcoholics. Fifty-six (18.7%) of the 300 patients had a family history of CHD, and 80 (26.7%) had a personal history of CHD. Table 2 shows the mean values and SD of all parameters studied in both groups. As expected, mean levels of inflammatory marker hs-CRP were significantly increased ($p < 0.001$) in ACS cases (9.15 ± 5.89 mg/L) when compared with the controls (1.08 ± 0.7 mg/L) (Fig. 1). As compared with controls, ACS patients also had significantly increased levels of TC (169.55 ± 24.46 *vs* 161.72 ± 17.64 mg/dL), TG (143.32 ± 48.97 *vs* 114.8 ± 24.67 mg/dL), LDL-C (100.01 ± 22.64 *vs* 89.22 ± 19.94 mg/dL), VLDL-C (28.58 ± 9.79 *vs* 22.96 ± 4.93 mg/dL), and ratios of TC:HDL-C (4.42 ± 1.33 *vs* 3.42 ± 0.89), and LDL-C:HDL-C (2.66 ± 1.04 *vs* 1.93 ± 0.74). There was a significant decrease observed in the mean level of HDL-C in ACS patients than controls (40.97 ± 10.26 and 49.48 ± 9.41 mg/dL) (Fig. 1).

In subgroup analysis, serum concentrations of hs-CRP were approximately 3-fold higher in group I when compared with the control group (3.4 ± 2.08 *vs* 1.08 ± 0.7 mg/L, $p < 0.001$), and the levels of hs-CRP were almost 12-fold higher in group II than the controls (12.98 ± 4.26 *vs* 1.08 ± 0.7, $p < 0.001$). Between ACS patients subgroups, serum hs-CRP levels were almost 4-fold higher in group II when compared with group I ($p < 0.001$). The serum levels of lipid profile were also significantly higher in group II when compared with group I and controls (except HDL-C, which is significantly decreased in group II than other groups) (Table 3 and Fig. 2).

Table 1: Demographic characteristic of ACS patients and controls

Parameters	*ACS patients (n = 300)*	*Controls (n = 100)*	*p value*
Age	59.08 ± 6.75	58.95 ± 7.59	>0.05[a]
Female/male	115/185	38/62	>0.05[b]
Body mass index (kg/m^2)	26.57 ± 3.99	25.1 ± 4.03	<0.01[a]
Hemoglobin (g/mL)	13.37 ± 2.23	14.11 ± 2.13	<0.05[a]
Hypertension, *n* (%)	125 (41.7)	41 (41)	>0.05[b]
Diabetes, *n* (%)	77 (25.7)	25 (25)	>0.05[b]
Smoking, *n* (%)	92 (30.7)	30 (30)	>0.05[b]
Alcohol, *n* (%)	88 (29.3)	28 (28)	>0.05[b]
Family history of CHD, *n* (%)	56 (18.7)	18 (18)	>0.05[b]
Personal history of CHD, *n* (%)	80 (26.7)	–	<0.001[b]

ACS, acute coronary syndrome; CHD, coronary heart disease.
[a]Independent sample *t*-tests
[b]Chi-square test

Table 2: Mean levels of hs-CRP and lipid profile in ACS patients and controls

Parameters	*ACS patients (n = 300)*	*Controls (n = 100)*	*p value*
hs-CRP (mg/L)	9.15 ± 5.89	1.08 ± 0.7	<0.001
TC (mg/dL)	169.55 ± 24.46	161.72 ± 17.64	<0.01
TG (mg/dL)	143.32 ± 48.97	114.8 ± 24.67	<0.001
LDL-C (mg/dL)	100.01 ± 22.64	89.22 ± 19.94	<0.001
HDL-C (mg/dL)	40.97 ± 10.26	49.48 ± 9.41	<0.001
VLDL-C (mg/dL)	28.58 ± 9.79	22.96 ± 4.93	<0.001
TC:HDL-C ratio	4.42 ± 1.33	3.42 ± 0.89	<0.001
LDL-C:HDL-C ratio	2.66 ± 1.04	1.93 ± 0.74	<0.001

ACS, acute coronary syndrome; hs-CRP, high-sensitive C-reactive protein; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol, VLDL-C, very-low-density lipoprotein cholesterol
Independent sample *t*-test was used

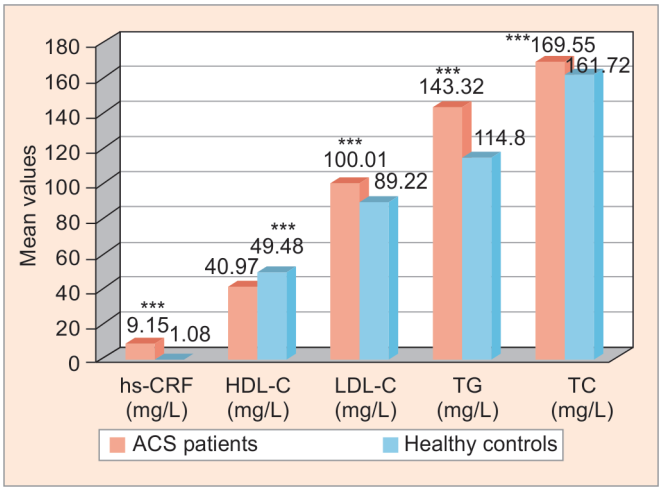

Fig. 1: Comparison of high-sensitive C-reactive protein (hs-CRP), and lipid profile levels in acute coronary syndrome patients and controls. Data are presented as mean values. $^{**}p < 0.01$, $^{***}p < 0.001$

Discussion

The present study showed that serum concentrations of hs-CRP were significantly increased in ACS patients than in controls, and patients have altered lipid parameters. In the subgroups of ACS, hs-CRP levels were significantly higher in patients with an onset of ACS ≥6 and <24 hours when compared with the patients with an onset of ACS <6 hours and controls. These findings indicate that increased levels of hs-CRP in group II are due to the result of myocardial damage. Our results are comparable to the finding of Cavusoglu et al.,[10] Yip et al.,[11] and Sheikh et al.[12] who demonstrated that the hs-CRP concentrations in patients presenting with ACS were significantly higher as compared to the controls.

Acute coronary syndrome is related to the inflammatory response and leads to the enhanced synthesis of acute-phase proteins, like CRP. Many studies have demonstrated that CRP is not only a marker of inflammation and inflammatory processes. C-reactive protein actively participates in both atherogenesis and atheromatous plaque disruption.[12] C-reactive protein decreases the synthesis of nitric oxide and prostacyclin and promotes endothelial dysfunction. Furthermore, it activates the classical complement system and expands tissue necrosis. Increased concentration of CRP levels during the acute phase of coronary events, start in the initial hours and peak around day 2.[13] Myocardial damage leads to the increased synthesis of pro-inflammatory cytokines, which interferes with the myocardium repairing processes and is also responsible for the severity of necrosis. High levels of cytokines lead to the increased production of CRP that binds to the myocardial cell membranes and activates the classical complement system. C-reactive protein stimulates the further inflammatory cascade, which leads to the damage of myocardial cells and the extension of tissue necrosis.[13]

It is well recognized that myocardial damage promotes the synthesis of CRP, and the level of CRP has been reported to be

Table 3: Comparison of all studied parameter between ACS patients subgroups; within 6 hours of onset of ACS (group I), and after 6 hours and within 24 hours of onset of ACS (group II) along with controls

Parameters	*<6 hours (group I) (n = 120)*	*≥6 hours to <24 hours (group II) (n = 180)*	*Controls (n = 100)*
hs-CRP (mg/L)	3.4 ± 2.08	12.98 ± 4.26^{III}	1.08 ± 0.7^{c,¶}
TC (mg/dL)	168.09 ± 22.44	170.53 ± 25.73	161.72 ± 17.64$^{\#}$
TG (mg/dL)	139.29 ± 50.92	146.01 ± 47.57	114.8 ± 24.67^{c,¶}
LDL-C (mg/dL)	96.9 ± 20.68	102.07 ± 23.69	89.22 ± 19.94^{a,¶}
HDL-C (mg/dL)	43.53 ± 10.89	39.26 ± 9.47 ^{II}	49.48 ± 9.41^{c,¶}
VLDL-C (mg/dL)	27.64 ± 10.16	29.2 ± 9.51	22.96 ± 4.93^{c,¶}
TC:HDL-C ratio	4.13 ± 1.25	4.61 ± 1.35 ^{II}	3.42 ± 0.89^{c,¶}
LDL-C:HDL-C ratio	2.43 ± 0.95	2.81 ± 1.07 ^{II}	1.93 ± 0.74^{c,¶}

ACS, acute coronary syndrome; hs-CRP, high-sensitive C-reactive protein; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol. Between groups I and II; $^{II}p < 0.01$, $^{III}p < 0.001$. Between group I and controls; $^{a}p < 0.05$, $^{c}p < 0.001$. Between group II and controls; $^{\#}p < 0.01$, $^{¶}p < 0.001$
One-way ANOVA test was used

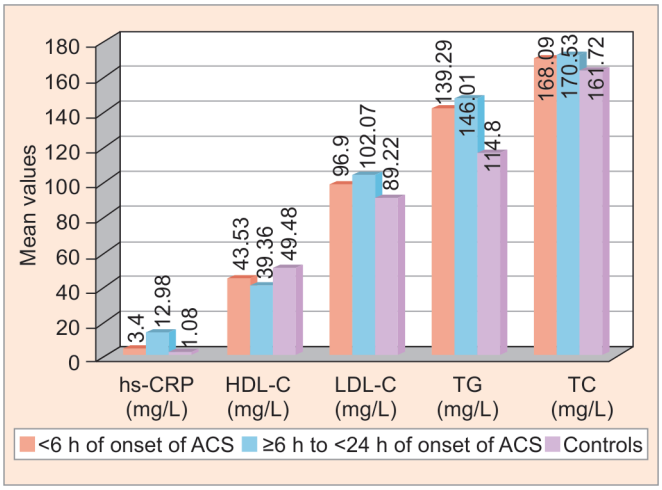

Fig. 2: Comparison of mean values of high-sensitive C-reactive protein (hs-CRP), and lipid profile levels between acute coronary syndrome (ACS) patients subgroups; within 6 h of the onset of ACS (group I), and after 6 h and within 24 h of the onset of ACS (group II) along with controls

associated with poor prognosis after ACS. However, CRP is primarily synthesized and secreted rapidly in the liver 6 hours after an acute inflammatory stimulus. Thus, serum levels of hs-CRP within 6 hours after the onset of ACS are suggested to offer valuable information with respect to cell biology activity on ruptured plaque without being affected by the effects of myocardial necrosis after AMI. Therefore, according to our study and other studies,[11] serum hs-CRP can be categorized into two different intervals in the clinical setting of ACS. This is of clinical importance because it may provide eligible information for the assessment of the possible impact of hs-CRP levels on coronary atherosclerotic lesions. The early phase of the inflammatory response is related to the ventricular function and remodeling, ischemia, and reperfusion injury, which can cause long-term events.[14] The Munich Myocardial Infarction Registry study emphasizes the importance of hs-CRP levels on admission with regard to the hospital outcome of diabetic and non-diabetic CHD patients.[15] He et al.[14] in a meta-analysis have quantitatively assessed the relation between early blood hs-CRP after ACS and risk of adverse outcomes in 20 longitudinal studies comprising 2,789 cases from 17,422 patients. They found that patients with higher hs-CRP levels of 3.1–10.0 mg/dL and >10.0 (mg/L) after ACS were associated with 1.4-fold and 2.18-fold higher risks of adverse outcomes when compared with the referent (CRP ≤3.0 mg/L). Thus, the measurement of hs-CRP at the time of admission in patients with suspected CHD may be helpful in identifying a group of patients who may be at high risk of cardiac complications and these patients need aggressive cardiac management and close monitoring after discharge.[12]

In subgroup analysis, we found significantly increased levels of TC, TG, LDL-C, and VLDL-C and ratios of TC:HDL-C and LDL:HDL-C and a decrease in HDL-C in group II than in patients with group I and controls**.** Dyslipidemia is an independent cardiac risk factor that contributes to the increased incidence of CHD. Epidemiological studies have conclusively linked high levels of LDL-C and low levels of HDL-C with CHD incidence and mortality. It is also well established that cholesterol plays an important role in the development of atherosclerosis, which is an underlying cause of CHD.[16] In a previous study, Gorecki et al.[17] observed higher levels of TC and LDL in patients with complicated *vs* those with the uncomplicated clinical course of infarction, suggesting higher levels of these biomarkers during the first 24 hours of AMI have a strong negative prognostic value. During tissue necrosis, acute phasic changes occur that alter the lipid profile levels post ACS. Therefore, the validity of plasma lipids measured beyond 24 hours from the onset of MI has been questioned by many studies.[18] Modifications of serum lipids after ACS include reductions in TC, LDL-C, and HDL-C in the range of 10–20%, with reciprocal increases in TG approximating 20–30%. The magnitude of the decrease in TC level after an MI is positively correlated with the infarct size and is not dependent on the patient's age or sex, the development of arrhythmias, or the development of heart failure.[18] These changes were believed to commence approximately 24 hours after the presentation and to last up to several months. Several mechanisms accounting for these changes include the acute phase response associated with upregulation of LDL-receptor activity and reduction in several pivotal HDL regulatory proteins. Based on these acute changes, the American College of Cardiology/American Heart Association has supported a Class I recommendation for a fasting lipid profile analysis to be obtained within 24 hours of admission for ACS.[19,20]

In conclusion, the results of the present study indicate that the levels of inflammatory marker hs-CRP are significantly elevated in ACS patients than in controls, and they have altered lipid profiles which may be responsible for the increased CHD mortality and morbidity. Our findings suggest that early estimation of hs-CRP is a valuable predictor for adverse outcomes in patients with ACS. Elevated levels of hs-CRP emerged as a reliable biomarker for the subclinical inflammatory state. Current evidence supports the usefulness of hs-CRP measurement for vascular risk and treatment efficacy assessment in CHD patients. Reliable knowledge of serum lipid levels early after admission to the hospital for an ACS can facilitate initiation of lipid-lowering therapy (most likely involving a statin), allow a more rational selection of drug dosage, and identify the potential need for adjunctive lipid-altering therapy.

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