

Association between hs-CRP levels and the severity of coronary atherosclerosis

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Objectives This study aimed to assess the relationship between serum inflammatory marker of high-sensitivity C-reactive protein (hs-CRP) with the presence and severity of angiographically evaluated coronary artery disease (CAD).

Methods This cross-sectional study was conducted in cardiac catheterisation unit at Al-Hussein Medical City, Al-Hussein Teaching Hospital/ Kerbala from November 2014 to September 2015. It included 76 patients (49 males and 27 females) who presented with the signs and symptoms of CAD and has undergone angiography. Serum levels of hs-CRP were measured in patients with CAD before entering into the catheterisation room. After coronary angiography was done for all patients, the extent and severity of CAD was correlated with serum levels of hs-CRP. The extent of CAD was determined by angiography according to the number of coronary arteries involved and degree of narrowing in coronary artery diameter. The serum level of hs-CRP was measured by ELISA technique.

Results The mean \pm SD age of patients was 57.76 ± 9.69 (ranged 35–79) years, 64.4% males and 35.6% females. Regarding the angiographic finding in patient group, it was normal in 22 patients (28.9%), single vessel involvement in 18 patients (23.7%), two vessels disease in 14 patients (18.4%) and three vessels disease in 16 patients (21.1%). The left main stem disease (LMD) was found in 6 patients (7.9%). The extent of CAD as obtained from angiographic finding had significant correlation with the serum level of hs-CRP ($r = 0.736$), ($P = 0.000000001$).

Conclusion There is a significant strong positive correlation between the extent of CAD and the serum level hs-CRP.

Keywords high sensitive C-reactive protein (hs-CRP), coronary arteries disease (CAD), body mass index (BMI)

Introduction

Coronary heart disease is the most prevalent chronic disease and the main leading cause of death in the world, with more than half a million newly diagnosed coronary artery disease (CAD) patients each year.^{1,2} Cardiac catheterisation and coronary angiography are often important for definitive evaluation of coronary artery anatomy, the presence of evaluation of CADs and the presence of interventional therapy.³

The use of biomarkers as a tool for the diagnosis of plaque rupture has generated great interest in clinicians due to their promise to either 'rule-in' or 'rule-out' acute coronary syndromes (ACS).⁴

There is strong evidence that cardiovascular conditions are linked to inflammation. Likewise, there is a role of inflammation in the pathogenesis of atherosclerosis.⁵ CRP is a sensitive, but non-specific acute-phase reactant, which (when elevated to ≥ 3 mg/L) is a predictor of cardiovascular events in otherwise asymptomatic individuals.⁶ Increases in CRP levels detected by assays with expanded sensitivity to very low levels of CRP, so-called high-sensitivity C-reactive protein (hs-CRP), showed a strong correlation as an independent risk factor for future cardiac events.

Importantly, CRP elevation is not only related directly to plaque burden, but also rather to plaque inflammation and instability. Though CRP can be elevated in other conditions, it possesses several traits that make it an attractive biomarker: (a) it is highly stable in plasma with a limited coefficient of variation, (b) it has been demonstrated to have predictive capacity in multiple ethnic groups, (c) it predicts both short- and long-term outcomes and (d) it provides independent predictive value in asymptomatic individuals, high-risk patients and also in disease states such as stroke, peripheral arterial disease and sudden death.⁷ Blood measurements of hs-CRP

are often performed to assess the risk of future heart disease. It has also been suggested that hs-CRP can be used to target therapy and tailor-risk modification to prevent cardiovascular disease (CVD).⁸ In most of the studies reported, the association of hs-CRP with cardiovascular risk has been found to be highly significant in global risk-assessment programmes.⁹

This study aimed to assess the relationship of serum inflammatory marker hs-CRP, with the presence and severity of angiographically evaluated CAD.

Materials and Methods

This study was conducted at the Departments of Medicine (angiographic department) in Al-Hussein Teaching Hospital/ Holy Kerbala, Iraq and in the Department of Biochemistry, College of Medicine, University of Kerbala from November 2014 to September 2015.

In this cross sectional study, 76 patients (49 males and 27 females) were studied who had undergone angiography and were found to have CAD. All the selected cases met the inclusion criteria of the study. Inclusion criteria consisted of adult patients of both sexes with ischemic heart disease, who had attacks of angina or myocardial infarction and had undergone coronary angiography. Exclusion criteria included stable angina, unstable angina, acute MI, acute or chronic renal diseases, thyroid disorders, recent stroke, diabetic ketoacidosis, non-ketotic hyperosmolar diabetes, any recent surgery in the last 2 months, tumours and autoimmune disease. Other parameters measured include blood sugar, blood pressure, age, gender and smoking state to compare the effect of these factors on the level of hs-CRP levels.

The classification of atherosclerotic patient depends on the extent of CAD. There are four main coronary arteries: left

main coronary artery, left anterior descending artery (LAD), left circumflex (LCX) and right coronary arteries (RCA) were assessed. All patients underwent coronary angiography, and the results were collected from the catheterisation laboratory according to the patient's name and file number. The angiographic results concern the presence of significant (lesions more than or equal to 70% diameter stenosis for coronary arteries and more than or equal to 50% diameter stenosis for left main coronary artery by visual estimation)¹⁰ coronary artery lesion and the numbers of arteries involved by a significant lesion and classified as:

- Normal (no significant lesion)
- left main stem (LMS) disease
- One vessel involvement
- Two vessels involvement
- Three vessels involvement.

After explaining the aims of the study and obtaining the patients' approval for participation, 1 mL blood samples were taken from the patients and were transferred to the laboratory after clotting, hs-CRP was measured using ELISA assay (hs-CRP ELISA Cat. No. DE740011).

Coronary angiography is performed under local anaesthesia. The procedure is sterile, and all potential access sites must be disinfected, shaved and sterilised. At the beginning of the procedure, the patient lies down in supine position on the cardioangiograph table, and is prepared for the procedure in sterile conditions. Coronary angiography is performed with the patient in the fasting state.

Results

The mean \pm SD of patient age was 57.76 ± 9.69 (ranged 35–79) years, in which 64.4% of males and 35.6% of females.

Regarding the angiographic finding in patient group, there was no significant finding in 22 patients (28.9%), single vessel involvement in 18 patients (23.7%), two vessels disease in 14 patients (18.4%) and three vessels disease in 16 patients (21.1%). The LMD was found in 6 patients (7.9%), while the remaining 70 patients (92.1%) were free of LMD. These findings are shown in Table 1.

The atherosclerotic patients presented with higher hs-CRP that mean significant correlation of the extent of coronary atherosclerosis disease with hs-CRP. There was no significant difference in hs-CRP titer between three vessel disease and LMD ($P = 0.903$). While, there is a significant difference of that titer between any two of the other angiographic findings ($P = 0.000000001$). There is strong positive association between the extent of CAD and hs-CRP titer ($r = 0.736$) as shown in Table 2.

Table 1. Angiographic findings of the studied group (N = 76)

Angiographic findings	No.	%
Non (normal or <70% stenosis)	22	28.9
One vessel disease	18	23.7
Two vessel disease	14	18.4
Three vessel disease	16	21.1
Left main stem disease (>50% stenosis)	6	7.9
Total	76	

There was a significant positive correlation between the extent of CAD and serum level of hs-CRP ($r = 0.736$), ($P = 0.000000001$) which means that the higher levels of hs-CRP are found in patients with more extensive CAD as shown in Table 3.

Discussion

The results obtained indicated that hs-CRP level is a good marker of the presence and extent of coronary atherosclerosis disease. This study was done to non-invasively assess the extent and severity of coronary atherosclerosis disease patients by measure serum level of hs-CRP. Numerous studies have provided the evidence that inflammation has important role in the occurrence and the development of coronary vessel disease.^{11–13}

The statical correlation between extent of CAD and level of hs-CRP are shown in Fig. 1. Accordingly, there are several mediators of the inflammatory response, including acute-phase

Table 2. The difference of hs-CRP titer between angiographic findings

Angiographic findings (hs-CRP mean \pm SD)		Significance of difference (P value)
No significant finding (1.01 \pm 1.07)	One vessel disease (2.64 \pm 2.14)	0.006
No significant finding (1.01 \pm 1.07)	Two vessel disease (4.33 \pm 2.01)	0.000
No significant finding (1.01 \pm 1.07)	Three vessel disease (6.01 \pm 2.14)	0.000
No significant finding (1.01 \pm 1.07)	Left main stem disease (6.12 \pm 1.68)	0.000
One vessel disease (2.64 \pm 2.14)	Two vessel disease (4.33 \pm 2.01)	0.012
One vessel disease (2.64 \pm 2.14)	Three vessel disease (6.01 \pm 2.14)	0.000
One vessel disease (2.64 \pm 2.14)	Left main stem disease (6.12 \pm 1.68)	0.000
Two vessel disease (4.33 \pm 2.01)	Three vessel disease (6.01 \pm 2.14)	0.014
Two vessel disease (4.33 \pm 2.01)	Left main stem disease (6.12 \pm 1.68)	0.049
Three vessel disease (6.01 \pm 2.14)	Left main stem disease (6.12 \pm 1.68)	0.903

Table 3. Correlation between hs-CRP titer and extent of CAD

Angiographic finding	No.	hs-CRP titer		P value (between groups)	Pearson r (correlation)
		Mean	Std. deviation		
Non	22	1.01	1.07		
One vessel disease	18	2.64	2.14		
Two vessel disease	14	4.33	2.01		
Three vessel disease	16	6.01	2.14	0.000000001	0.736
Left main stem disease	6	6.12	1.68		
Total	76	3.46	2.68		

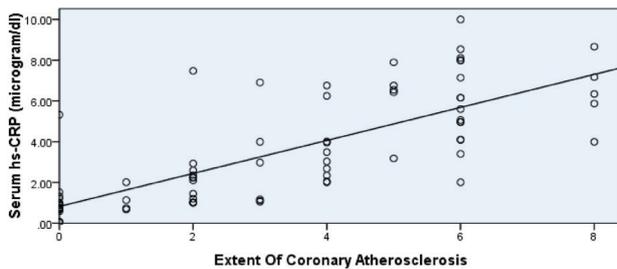


Fig. 1 Correlation between extent of CAD and level of hs-CRP.

proteins, cytokines and cellular adhesion molecules have been evaluated as potential indicators of the risk of a first acute atherothrombotic event, as well as of recurrent complications after initial presentation.¹⁴ As the prototypical acute-phase reactant, hs-CRP has been the focus of much of the clinical investigation.¹⁵ This can be explained as that, hs-CRP is an acute-phase protein marker that can demonstrate the subclinical inflammatory states detecting lower serum levels of CRP. There are several advantages in hs-CRP measurements related to coronary vessel disease. The first advantage is that, it is a stable compound, and it can be measured at any time of the day without special relevance to biological clock of the day.¹⁶ While, the other markers such as lipids and IL-6 exhibit circadian rhythm and are related to meals also. Thus, we can perform hs-CRP testing in clinical settings at any time in a day.¹⁷

Cushman et al. have reevaluated the prevalence and correlates between increased hs-CRP and reported a significant effect of hs-CRP measurement on coronary heart disease risk reclassification. They observed that with the inclusion of hs-CRP in

their testing data, the Reynolds risk score classified the population differently compared to the new Framingham risk scores.¹⁸

This observation is in agreement to our study regarding hs-CRP and its significant correlation with the presence and the severity of coronary vessel disease.¹⁹

The publication of that article as this study was being performed indicates the novelty of the subject. In another study performed on 140 patients with CAD in India, the researchers found a positive correlation between the serum levels of hs-CRP and the severity of coronary atherosclerosis in the patients without diabetes mellitus and since only non-diabetic patients who had coronary atherosclerosis were studied, the findings could not be generalised.²⁰

To the best of our knowledge, no such study has been done in Iraq till now. The novelty of our study, its controversy and its strength concerning the effect of regional factors with the regard to life conditions make the study distinguished.

The possible limitations of our study are limited the number of subjects and cross-sectional design. The prospective studies on large scale are needed to explore the true pathogenic role of hs-CRP in assessing cardiovascular risk as not indicator for atherosclerotic extent. Additionally, the study was carried out in a tertiary center, so the findings could not be generalised to the whole population.

Conclusion

We conclude that the coronary atherosclerosis patient has high level of hs-CRP on comparing with healthy people. Also the level of the increase in hs-CRP indicates the level of CAD extent. ■

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