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Association between Serum Levels Of Hs-CRP and LDL-C with Degree of Coronary Artery Stenosis in Patients with Stable Angina Pectoris

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Abstract

Background: Over the past decade, several studies have revealed the role of high sensitivity C-reactive protein (hs-CRP), an acute inflammatory marker, as a prognostic factor in the setting of myocardial infarction, predicting future cardiac outcome of patients suffering from an acute coronary event. This study compares hs-CRP and low density lipoprotein-cholesterol (LDL-C) in predicting degree of coronary stenosis in patients with chronic stable angina.

Methods: One hundred and five patients with chronic stable angina undergoing angiography were evaluated regarding known cardiovascular risk factors including age, sex, smoking habit, exercise, parental history of premature CAD, history of diabetes mellitus, hyperlipidemia, and hypertension, total-cholesterol, LDL-C, HDL-C and triglyceride. hs-CRP was measured by nephlometery and degree of coronary involvement was quantified by using an angiographic scoring scale.

Results: Results showed that hs-CRP was not correlated with angiographic score. When all traditional risk factors were entered as independent variables, age, sex, and history of hyperlipidemia were significant predictors of degree of coronary stenosis, and neither hs-CRP nor LDL-C were statistically significant. It was shown that hs-CRP was only related to sex and HDL-C.

Conclusion: We conclude that larger studies with better set points for hs-CRP should be conducted, but our study indicates that traditional CAD risk factors including age, sex and history of hyperlipidemia still predict degree of coronary artery stenosis better than hs-CRP and hs-CRP measurement doesn't add any information in this regard. Association of low HDL and hs-CRP may warrant further studies, too.

Keywords: hs-CRP; LDL-C; Coronary artery stenosis; Stable angina pectoris

Introduction

Cardiovascular disease (CVD) is common in the general population, affecting the majority of adults beyond 60 years. The lifetime risk of coronary heart disease (CHD) as illustrated in the Framingham Heart Study[1] for individuals at age 40 was 49% in men and 32% in women. Even men and women free from disease at age 70 had a lifetime risk of 35% and 24%, respectively. No other life-threatening disease is as prevalent or expensive to the society. Many of the important risk factors for cardiovascular disease are modifiable by specific preventive measures. In the worldwide INTERHEART study of patients from 52 countries, nine potentially modifiable factors accounted for over 90% of the population attributable risk of a first MI.[2] These included smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, lack of daily consumption of fruits and vegetables, regular alcohol consumption, and lack of regular physical activity.[3,4]

Experimental and clinical evidence accumulated since 1990 have established inflammatory processes as important contributors to atherogenesis as well as the vulnerability of an atherosclerotic lesion to rupture or erosion. Based upon this evidence, protein markers of inflammation have been studied as

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noninvasive indicators of underlying atherosclerosis in apparently healthy individuals. The most extensively studied biomarker of inflammation in cardiovascular disease is serum C-reactive protein (CRP), for which standardized high-sensitivity assays (hs-CRP) are widely available.[5,6] CRP is an acute phase protein that is produced predominantly by hepatocytes under the influence of cytokines such as interleukin 6 and tumor necrosis factor-alpha.[7]

The mechanisms responsible for the association between CRP and cardiovascular disease are not clear. CRP may be only a marker of inflammation and thrombotic risk, without any specific role in the degree of atherosclerosis[8,9] or it may have a direct effect. The following observations suggest that there may be a direct effect: i) CRP has been found in atherosclerotic lesions, ii) CRP binds to low density lipoprotein (LDL), allowing LDL to be taken up by macrophages without the need for modification,[7] and iii) Administration of CRP promotes inflammation in humans and atherosclerosis in an animal model.[10,11]

Various studies have found that CRP is a determining factor in plaque rupture,[12-13] prognosis after non-ST elevation MI,[14-18] recurrent in-hospital cardiac event,[13] long term mortality after MI,[19,20] and recurrent ischemic event after coronary artery bypass grafting.[21] Also, among patients with known stable coronary disease, a strong positive correlation between CRP measured at baseline and future acute coronary events has been demonstrated in most studies,[22-27] but hs-CRP is only weakly associated with the extent of coronary disease on angiography[22,28] and the degree of coronary artery calcification on electron beam CT.[29] However, results from these studies cannot be directly compared as cut points for CRP levels differed from study to study.

Traditional methods for measuring serum CRP were developed for use in patients with infectious and inflammatory disorders. These assays typically have a detection limit in the range of 3 to 5 mg/L, which is above the concentration observed in most apparently healthy individuals. High sensitivity methods for measurement of CRP (hs-CRP) detect concentrations down to 0.3 mg/L. The assays are necessary for cardiovascular risk stratification, which is based upon discrimination of CRP levels extending below 3 mg/L.

The value that constitutes an elevation in serum hs-CRP is not clearly defined.[6,30] A statement from the Centers for Disease Control and Prevention and the American Heart Association (CDC/AHA) reached the following conclusions for the use of serum hs-CRP to estimate cardiovascular risk:[30] i) The average of two assays, fasting or non-fasting, and optimally obtained two weeks apart provide a more stable estimate than a single measurement, ii) For the determination of cardiovascular risk, low, average, and high risk values were defined as <1, 1 to 3, and >3 mg/L; these values correspond to approximate tertiles in the general population. It was suggested that a value above 10 mg/L should initiate a search for a source of infection or inflammation. The measurement of hs-CRP should be repeated in two weeks and iii) Among patients with known coronary heart disease (CHD), it was suggested that a value >3 mg/L is appropriate for predicting outcomes in patients with stable CHD and that a threshold >10 mg/L may be more predictive in patients with an acute coronary syndrome.

In a large study using the above recommendations from the CDC/AHA, 3771 patients with stable coronary artery disease in the PEACE trial were evaluated.[31] Patients had hs-CRP measured at baseline and were followed for outcomes of cardiovascular death, MI or stroke over a mean follow-up of 4.8 years. The following findings were noted: i) Across all measured subgroups, including men and women, patients on or off statin therapy, and patients with or without prior coronary revascularization, higher baseline hs-CRP levels were associated with significantly a higher rate of cardiovascular events compared to those with hs-CRP <1 mg/L (hs-CRP 1 to 3 mg/L: adjusted hazard ratio [HR] 1.39, 95% CI 1.06-1.81; hs-CRP >3 mg/L: adjusted HR 1.52; 95% CI 1.15-2.02) and ii) An elevated hs-CRP was predictive of the development of heart failure and new diabetes. In addition, serum CRP may predict coronary disease progression[32] and coronary disease with inducible ischemia on stress testing.[33]

Despite abundant studies, there is still a debate in scientific societies whether inflammation is a chronic process leading to atherosclerosis or it is an acute response to plaque rupture, the main pathogenic event in acute coronary syndrome. We decided to conduct a study to evaluate the role of CRP in prediction of degree of coronary stenosis in patients with chronic stable angina and compared CRP to other established CHD risk factors to see whether it has an independent role after adjustment for other risk factors.

Materials and Methods

The study population was selected from patients who underwent angiography for chronic stable angina in

three cardiovascular centers including Nemazee, Faghihi, and Kowsar hospitals in Shiraz, southern Iran from March 2007 to March 2008. This study was approved by local ethical committee. Chronic stable angina was suspected by history and laboratory tests and the following inclusive and exclusive criteria were implemented (Table 1).

Table 1: Inclusion and exclusion criteria for patient selection in association of Hs-CRP and CAD in stable angina patients

Inclusion criteria	Exclusion criteria
1- Chest pain during exercise 2- Chest pain after meal 3- Positive exercise test	1- Chest pain at rest 2- MI in previous 3 months 3- surgery in previous 3 months 4- previous CABG or PCI 5- history of chronic inflammatory disease (Ex. Systemic lupus erythematosus) 6- ST elevation in electrocardiogram 7- positive cardiac enzymes 8- Acute inflammatory illness in previous 3 days(Ex. Common cold) 9- Clinically unstable patients 10- EF< 30%

A hundred and five patients fitted these criteria and were included in the study. All these patients were fasted overnight, and in the morning, at the time of angiography blood samples were taken. Samples were allowed to form clot at room temperature, then they were transferred to laboratory on ice, where they were centrifuged at 2500 cycles per minute within half an hour, being divided into aliquots and stored at -20^0C until time of analysis. All samples were tested for CRP, total cholesterol, LDL-C, HDL-C and triglyceride (TG).

All patients had submitted their written consent. Angiographies were performed according to the standard Judkins technique. The degree of coronary artery involvement was quantified by using an angiographic scoring scale, which quantified intensity of involvement of eight major coronary branches at the point of maximum stenosis and the numbers were added together to form the angiographic score for each individual.

Angiography films were reported by a single cardiologist who was blinded to lab results. Based on Gensini scoring, eight major coronary arteries including left main stem, left anterior descending, diagonal branch, 1st septal perforator, left circumflex artery, marginal or posterolateral branch, right coronary artery and main posterior descending artery were evaluated for degree of stenosis and the narrowest part of each artery was scored 0 for no stenosis; 1 for 1-49% stenosis; 2 for 50-74% stenosis; 3 for 75-99% stenosis and 4 for total occlusion. The points for all vessels were added together and an angiographic score between 0-32 was assigned to each individual.

In order to decrease visual error ultimately the patients were divided into six categories on the basis of their angiographic scores. Those with angiographic score (0-4) labeled as group 1, (5-8) group 2, (9-12) group 3, (13-16) group 4, (17-20) group 5, and above 21 group 6.

The study population was also evaluated for other known risk factors for CAD including age, sex, smoking habit, exercise, parental history of premature CAD (male<45 or female<55), history of diabetes mellitus, history of high blood cholesterol whether controlled by diet or medication, level of blood pressure: hypertensive (systole≥140 or diastole≥90 or using medication), prehypertensive (120≤Systole<140 or 80≤diastole<90) and normotensive (systole<120 and diastole<80).

Serum CRP concentrations were measured by a highly sensitive nephlometric method (MININEPH™ human C-reactive protein kit; The Binding Site Ltd., Birmingham, UK). The principle of nephlometry involves determination of soluble antigen concentration after it forms insoluble complexes with antibodies bound to latex particles. When light is passed through the suspension, a portion of light is scattered and detected by a photodiode. The amount of light scattered is directly proportional to the specific protein concentration in the test sample. Concentrations are automatically calculated by reference to a calibration curve stored within the instrument.

In order to measure CRP, the samples were diluted to the concentration of 1/40 using MININEPH sample diluent. A MININEPH curette containing a stirring bar and 20 µl of the diluted sample was placed in the curette chamber then 400 µl of MININEPH CRP Buffer and 40 µl of MININEPH Hu CRP Reagent were dispensed into the curette. It took 30 seconds and the result was displayed and printed out. The approximate measuring range was 0.3-11.2 mg/dl. The sensitivity was 0.044 mg/dl when using a 1/5 sample dilution. CRP levels were divided into three categories:

CRP ≤ 0.3 mg/dl as low, 0.3 < CRP ≤ 1 mg/dl as borderline and CRP > 1 mg/dl as high.

T-chol, LDL-C, HDL-C and TG were measured enzymatically, using Pars-Azmoon test kits (Pars-Azmoon, Karaj, Iran).

The data were analyzed with the SPSS for windows statistical package version 14, and were presented as Mean±SD for continuous variables and frequency and percentile for categorical variables. The angiographic score was considered the dependent variable and age, sex, smoking habit, exercise, parental history of premature CAD, history of diabetes mellitus, hyperlipidemia, hypertension, CRP, T-chol, LDL-C, HDL-C and TG were the independent variables. To estimate the independent predictive value of each parameter, all variables were analyzed using multiple regression.

Comparisons between qualitative variables were performed using the Chi-square test. Comparison of continuous variables between six angiographic groups was performed by the One-way analysis of variance (ANOVA) test. The level of significance was set at 5% in all tests.

Results

The distribution of the study population between different angiographic groups are shown in Table 2 and the distribution of cardiovascular risk factors among different angiographic scores and whether they have a statistically significant correlation with angiographic score are shown in Table 3.

Table 2: Distribution of the study population between different angiographic groups in study of association of Hs-CRP and CAD in stable angina patients.

Angio Score	Frequency	Percentage
1	24	22.9
2	25	23.8
3	24	22.9
4	15	14.3
5	9	8.6
≥6	8	7.6
Total	105	100

Amongst the independent variables only age and sex demonstrated a statistically significant correlation with the angiographic score as is shown in table 3 (p=0.013 and 0.021, respectively). Although CRP is not related to angiographic score at 5% significance level (p=0 .061), there is a trend toward increased angiographic score in patients with higher CRP level (Figure 1), which might have reached statistical significance if the sample size was larger.

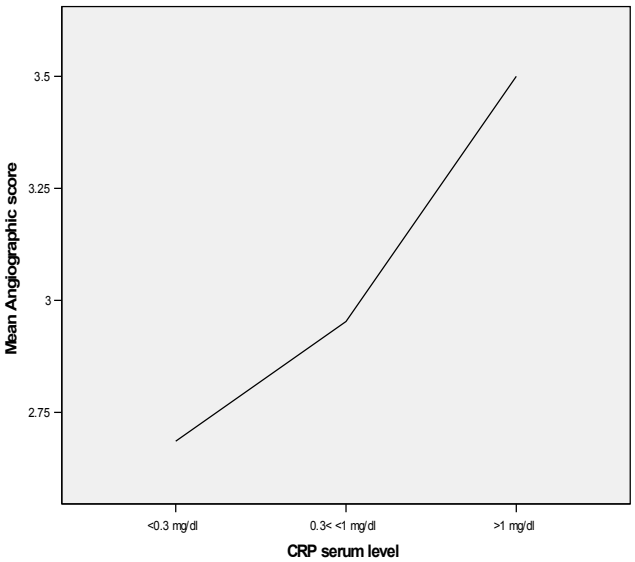

Fig. 1: Distribution of mean angiographic scores between different CRP groups in Hs-CRP and CAD association in stable angina patients

In linear regression analysis, in which the angiographic score was the dependent variable and all the risk factors including, age, sex, smoking habit, exercise, parental history of premature CAD, history of diabetes mellitus, hyperlipidemia, hypertension, CRP, T-chol, LDL-C, HDL-C and TG levels, were the independent variables, only sex, age, and hyperlipidemia were statistically significant predictors of angiographic score (p=0.0001, R square=0.347). Standardized Coefficient (ß) for sex, age, and hyperlipidemia were 0.375, 0.356 and 0.194, respectively, which revealed that sex is stronger than age and age is stronger that hyperlipidemia in predicting angiographic score (Table 4). This study reveals that both CRP and LDL-C are insignificant predictors of angiographic scores after adjustment for other risk factors (p value 0.324 and 0.806, respectively).

We also evaluated the relationship between CRP level and other risk factors of coronary artery disease. The results revealed that amongst the risk factors only age and HDL-C level (Figure 2) have statistically significant correlation with serum CRP level (p=0.05 and 0.013, respectively).

Table 3: Demographic and baseline characteristics of study population in different groups with different angiographic scores, in association of Hs-CRP and CAD in stable angina patients.

Angio Score	1	2	3	4	5	≥6	*P* value
Age	54.5±11†	52.2±8.6	56.6±9.8	57.0±8.0	66.5±8.7	60.5±13.6	0.013
Sex							0.029
F	18 (75%)‡	13(52%)	10 (41.7%)	8 (57.1%)	3 (33.3%)	1 (12.5%)	
M	6 (25%)	12 (48%)	14 (58.3%)	6 (42.9%)	6 (66.7%)	7 (87.5%)	
Smoking							0.948
No	10 (41.7%)	14 (56%)	14 (58.3%)	7 (46.7%)	5 (55.6%)	4 (50%)	
<10	8 (33.3%)	6 (24%)	4 (16.7%)	3 (20%)	3 (33.3%)	2 (25%)	
>10	6 (25%)	5 (20%)	6 (25%)	5 (33.3%)	1 (11.1%)	2 (25%)	
Exercise							0.203
No	24 (100%)	24 (96%)	24 (100%)	13 (86.7%)	8 (88.9%)	8 (100%)	
Yes	0 (0%)	1 (4%)	0 (0%)	2 (13.3%)	1 (11.1%)	0 (0%)	
Family Hx							0.700
No	18 (75%)	22 (88%)	18 (75%)	11 (73.3%)	6 (66.7%)	7 (87.5%)	
Yes	6 (25%)	3 (12%)	6 (25%)	4 (26.7%)	3 (33.3%)	1 (12.5%)	
DM							0.288
No	21 (87.5%)	17 (68%)	15 (62.5%)	9 (60%)	6 (66.7%)	7 (87.5%)	
Yes	3 (12.5%)	8 (32%)	9 (37.5%)	6 (40%)	3 (33.3%)	1 (12.5%)	
HTN							0.635
No	9 (37.5%)	12 (48%)	11 (45.8%)	7 (46.7%)	4 (44.4%)	4 (50%)	
Prehyper	2 (8.3%)	6 (24%)	6 (25%)	5 (33.3%)	2 (22.2%)	2 (25%)	
Yes	13(54.2%)	7 (28%)	7 (29.2%)	3 (20%)	3 (33.3%)	2 (25%)	
HLP							0.657
No	13 (54.2%)	9 (36%)	12 (50%)	4 (26.7%)	3 (33.3%)	2 (25%)	
Diet	11 (45.8%)	15 (60%)	11 (45.8%)	10 (66.7%)	6 (66.7%)	5 (62.5%)	
Med	0 (0%)	1 (4%)	1 (4.2%)	1 (6.7%)	0 (0%)	1 (12.5%)	
CRP							0.061
0.3	18 (75%)	19 (76%)	12 (50%)	13 (86.7%)	4 (44.4%)	4 (50%)	
0.3< ≤ 1	4 (16.7%)	5 (20%)	7 (29.2%)	1 (6.7%)	1 (11.1%)	3 (37.5%)	
>1	2 (8.3%)	1 (4%)	5 (20.8%)	1 (6.7%)	4 (44.4%)	1 (12.5%)	
T-Chol	172.8±33	172.8±48	175.3±49	187.6±46	167.5±29	145.2±55	0.428
LDL-C	94.1±20.7	90.1±28	91.4±32.3	107.4±32	92±22.3	82.1±33.8	0.378
HDL-C	37±10.8	35.2±11	35.6±13.8	35.8±7.5	34.1±8.6	33±15.4	0.965
TG	143.2±52	156.9±61	144.2±59	128.3±60	154.3±74	127.7±69	0.698

*P values are calculated from Chi-square test for categorical variables and from ANOVA for continuous variables.
†Continuous variables are given in Mean± SD. ‡ Categorical variables are given in absolute and relative frequencies.

Table 4: Linear regression analysis of study population in association of Hs-CRP and CAD in stable angina patients

Variable	Unstandardized Coefficient(B)	Standardized Coefficient(ß)	*P* value
Age	0.052	0.356	0.001*
Sex	1.149	0.375	0.0001*
Smoking	-0.145	-0.076	0.425
Exercise	0.111	0.015	0.879
Family Hx	0.229	0.063	0.537
DM	0.545	0.164	0.107
HTN	-0.231	-0.131	0.232
HLP	0.532	0.194	0.057*
CRP	0.230	0.101	0.324
T-Chol	-0.002	-0.061	0.810
LDL-C	0.003	0.053	0.806
HDL-C	-0.017	-0.121	0.306
TG	-0.002	-0.091	0.517

*Only Age, Sex and Hyperlipidemia are significant predictors of angiographic score (P<0.05).

Table 5: Correlation between serum CRP level and other known CAD risk factorsin study of association of Hs-CRP and CAD in stable angina patients.

CRP serum level		<0.3 mg/dl	0.3<<1mg/dl	>1 mg/dl	*P* value
Age		55.73±10.2	57.21±10.5	59.45±12.7	0.524*
Sex	F	39 (56.5%)	11 (52.4%)	3 (21.4%)	0.05†
	M	30 (43.5%)	10 (47.6%)	11 (78.6%)	
Smoking	No	38 (54.3%)	11 (52.4%)	5 (35.7%)	0.176
	<10	19 (27.1%)	2 (9.5%)	5 (35.7%)	
	>10	13 (18.6%)	8 (38.1%)	4 (28.6%)	
Exercise	No	67 (95.7%)	20 (95.2%)	14 (100%)	0.723
	Yes	3 (4.3%)	1 (4.8%)	0 (0%)	
Family Hx	No	56 (80%)	16 (76.2%)	10 (71.4%)	0.757
	Yes	14 (20%)	5 (23.8%)	4 (28.6%)	
DM	No	53 (75.7%)	11 (52.4%)	11 (78.6%)	0.095
	Yes	17 (24.3%)	10 (47.6%)	3 (21.4%)	
HTN	No	31 (44.3%)	9 (42.9%)	7 (50%)	0.977
	Prehyper	16 (22.9%)	4 (19%)	3 (21.4%)	
	Yes	23 (32.9%)	8 (38.1%)	4 (28.6%)	
HLP	No	28 (40%)	10 (47.6%)	5 (35.7%)	0.629
	Diet	38 (54.3%)	11 (52.4%)	9 (64.3%)	
	Med	4 (5.7%)	0 (0%)	0 (0%)	
T-Chol		173.53±41.8	173.76±46.7	169.08±56.2	0.944
LDL-C		93.67±27.1	97.52±26.9	85.57±37	0.475
HDL-C		35.91±9.7	36.48±11.9	27.36±14.6	0.013†
TG		144.43±58	133.81±46.1	159.79±83	0.455

*P values are calculated from Chi-square test for categorical variables and from ANOVA for continuous variables.
†Only 2 variables showed significant correlation with serum CRP level (p<0.05)

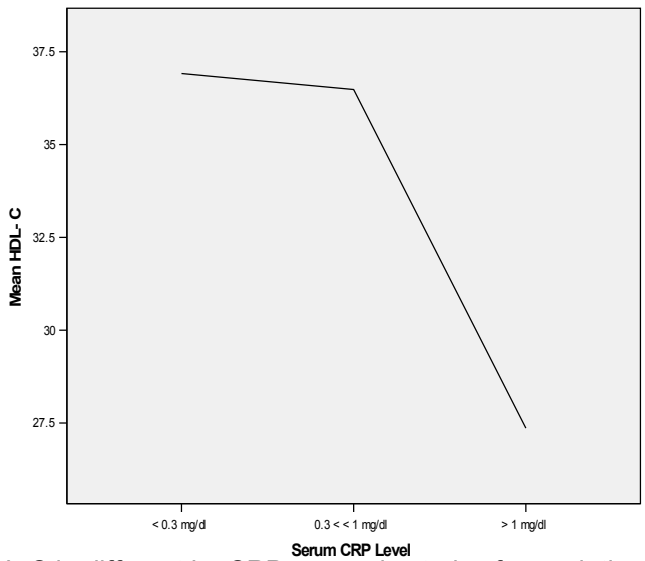

Fig. 2: Distribution of mean HDL-C in different hs-CRP groups in study of association of Hs-CRP and CAD in stable angina patients

Discussion

Most of the studies done before in patients with chronic stable angina are prospective studies on role of serum CRP in predicting future cardiac prognosis and risk of acute coronary event, but this cross-sectional study was designed to see whether CRP, as a marker of inflammation, can predict degree of coronary stenosis in patients with chronic stable angina and whether it is an independent predictor after adjustment for other traditional CAD risk factors.[8,22,29]

There were several limitations in measuring hs-CRP that need consideration. The normal range of CRP has been reported as 0.08 to 3.1 mg/l, with a median of approximately 1.5 to 2.2 mg/l.[34,37] Analysis of blood samples in a large-scale study in the United States showed a highly skewed distribution of CRP ranging from 0.1 to 296.0 mg/l. In that study 51% of adults had CRP levels above 2 mg/l, 39% had levels above 3.0 mg/l and 10% were above 10 mg/l. Within-subject variability has also been reported for CRP and varies from 30 to 63%, with a correlation coefficient of 0.6.[35] Given the high biologic variability and the possible effects of asymptomatic inflammation, measurements taken 2 weeks apart are recommended for classification of individuals into cardiovascular risk categories.[36]

In the current study we had a single measurement of hs-CRP which is not very accurate and although in many of previous studies hs-CRP was categorized as we did, considering the normal distribution of CRP, it would have been better if we divided CRP levels into to the following three categories: CRP ≤1 mg/l, 1≤ ≤3 mg/l and ≥3 mg/l.

In the present study we detected a trend toward increased CRP level in patients with higher angiographic scores and we strongly believe larger studies with better categorization of CRP level are required to explore whether CRP is correlated with degree of coronary stenosis in patients with chronic stable angina.

W Koenig and colleagues have managed to show in a large prospective study with 936 participants that CRP remains a strong independent predictor of adverse heart event after adjustment for traditional CAD risk factors.[38] They used fatal or nonfatal MI and sudden cardiac death occurring before age of 75 as the outcome variable. Nevertheless, in our cross-sectional study we did not detect a relationship between angiographic score and CRP level after adjustment for other risk factors of CAD. It should be noted that there are fundamental differences between the studies as Koenig's study was limited to middle aged men, and the researchers used the very sensitive immunoradiometric assay to measure CRP concentration, which yields one decimal place more than that in the nephlometric assay. Furthermore, the Koenig's study outcome variables were acute coronary syndromes and were studied prospectively in a population who did not experience previous MI., whereas we evaluated the association between CRP and degree of coronary artery disease in patients with stable angina pectoris.

In linear regression analysis in which angiographic score was the dependent variable and age, sex, smoking habit, exercise, parental history of premature CAD, history of diabetes mellitus, hyperlipidemia, and hypertension, T-chol, LDL-C, HDL-C, TG and hs-CRP were the independent variables, it was revealed that only age, sex, and hyerlipidemia were significant independent predictors of angiographic score (*p* value 0.001, 0.0001 and 0.057) and after adjustment for traditional CAD risk factors neither hs-CRP nor LDL-C (P-value 0.324 and 0.806, respectively) was found to be statistically significant predictors of degree of coronary stenosis. The question is why CRP didn't appear a significant independent predictor in linear regression analysis in spite of having correlation with angiographic score at P-value = 0.061. We assume that since sex is the strongest predictor of degree of coronary stenosis and it is also significantly correlated with hs-CRP, it masked the effect of hs-CRP in multivariate analysis and so hs-CRP did not appeare as an independent predictor of degree of coronary stenosis.

Our results also indicated that male patients had a significantly higher CRP levels comparing to females. Guran O and colleagues have previously shown that children with risk factor for CAD have higher serum hs-CRP than those with no risk factor and serum CRP level correlated with BMI, diastolic blood pressure, fibrinogen and HDL-C level but Age, Systolic blood pressure, LDL-C, TG were not related to CRP.[39,40]

Another notable finding was that Hs-CRP was inversely correlated with HDL-C serum level (Figure 2). This indicates that Low HDL-C, which is a proven risk factor for CAD, may also be a marker of inflammation in general population and warrants further studies to evaluate the effect of inflammation in HDL-C and its effect on severity and progression of CAD.

Although our study managed to show an association between hs-CRP level and degree of coronary

artery disease at *p* value .061, this association disappeared in multivariate analysis, and still traditional risk factors such as age, sex and hyperlipidemia were the significant determinants of the degree of coronary artery involvement in regression analysis. Nevertheless, some other well-proven risk factors of CAD such as smoking, exercise, and history of diabetes also failed to show an association with the degree of coronary involvement. Hence the lack of association between levels of CRP and degree of coronary disease does not rule out its possible role in inflammation and consequently plaque rupture since these are acute and abrupt events and might have no relation with the already stable coronary stenosis.

We suggest that future studies evaluating the association between inflammation and coronary artery disease apply more accurate techniques for measuring CRP levels that can detect CRP level between 0.3-10 mg/L; such as radioimmunoassay or ELISA methods or even better use other indicators of inflammation that are less variable and hence more reliable. Since inflammation is demonstrated to provide a ground for plaque rupture, it seems to be more appropriate that future studies focus on the association between markers of inflammation and acute coronary events rather than stable angina.

Small number of patients and one time check of Hs-CRP were main limitations of this study. Further studies with larger number of patients with several times check of Hs-CRP can shed light on this complex dilemma. Traditional CAD risk factors, including age, sex and hyperlipidemia predict severity of coronary artery involvement, better than Hs-CRP, and this index does not add any information in this regard. Association of Hs-CRP and low HDL would warrant further studies.

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Conflict of interest: None declared.

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