ORIGINAL RESEARCH PAPER

Cardiology

STUDY ON RELATIONSHIP BETWEEN HIGH SENSITIVITY CRP AND ANGIOGRAPHIC SEVERITY OF CAD

KEY WORDS: hs-CRP, Coronary artery disease, Angiographic stenosis, Angiographic extent

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ABSTRACT

Objective: (A) To study the levels of hs-CRP in patients with angiographically documented acute coronary syndrome (ACS), chronic coronary artery disease (chronic CAD) (B) To compare angiographic stenosis and extent score with hs-CRP levels in patients with ACS and chronic CAD.

Methods: A total of 80 patients who were admitted for coronary angiography with the diagnosis of ACS/chronic CAD were included in this study. The quantitative hs-CRP levels were measured by immunoturbidometry method. Gensini scoring was performed to measure the stenosis score and extent score. Later, the levels of hs-CRP were compared with the stenosis and extent score in angiographically documented CAD. Data was analyzed using Statistical Package for the Social Science (SPSS) Version 11.5

Results: There was statistically significant hs-CRP elevation in angiographically confirmed CAD patients . It was found that hs-CRP levels were much higher in acute coronary syndrome patients. The hs-CRP levels were found to be in direct proportion to extent score of coronary artery disease . Also, angiographic stenosis score was found to be higher in patients with higher hs-CRP levels .

Conclusion: Significant correlation was observed between the extent of coronary artery disease and hs-CRP levels. Similarly hs-CRP levels were found to be higher in patients with higher degree of angiographic stenosis. This shows that hs-CRP levels have a correlation with the disease burden in CAD patients.

INTRODUCTION

C-reactive protein is the prototypic marker of inflammation in humans and a member of a highly conserved family of proteins called the pentraxins. CRP is predominantly synthesized in hepatocytes as an acute-phase reactant and is transcriptionally driven by IL-6, with synergistic enhancement by IL-1. Serum high sensitivity C-reactive protein hs-CRP, a biomarker of inflammation, has been shown to effectively predict the risk of adverse cardiovascular (CV) events consistently[1]. Indian population have a predilection for CAD in younger age[2]. The ability of hs-CRP to add to the predictive capacity of other established risk factors has been examined in several studies. Through stratification or multivariable statistical adjustment, hs-CRP retains an independent association with incident coronary events after adjusting for age, total cholesterol, HDL cholesterol, smoking, body mass index, diabetes , history of hypertension, exercise level, and family history of coronary disease. Coronary atherosclerosis is the main substrate of adverse coronary events and serum hs-CRP levels may act as an indirect measure of its extent within the coronary vasculature. This may prove to be an inexpensive screening tool in CV risk assessment. Limited information is available regarding the correlation between serum hs-CRP levels and the extent and severity of CAD, as assessed by Gensini score in patients submitted to coronary angiography. A growing number of studies have examined inflammatory markers as predictors of recurrent CVD and death in different settings, including the short-term risk, long-term risk, and risk after revascularization procedures such as percutaneous coronary intervention (PCI), including the risk of restenosis. Although several markers have been studied, the strongest association with prognosis has been with fibrinogen and hs-CRP. It consistently predicts new coronary events in patients with unstable angina and acute myocardial infarction[3,4,5]. Most of these studies have been long term, but some in-hospital survivorship studies [6,7,8,9] have also shown an association. We carried out a study to assess the correlation between plasma hs-CRP levels with severity of coronary atherosclerosis. The aim was to correlate the levels of hs-C reactive protein with angiographic severity of coronary artery stenosis in patients with Ischaemic heart disease, admitted for Coronary Angiography in Madras Medical College during August 2016 to April 2017.

MATERIALS AND METHODS

This is an observational study included 80 patients undergoing diagnostic coronary angiography at the Institute of Cardiology, Madras Medical College,Chennai. All patients of IHD admitted for Coronary Angiography in our institute during August 2016 to April 2017. Patient with past CABG, PTCA, valvular heart disease , hepatic dysfunction, major non-cardiovascular disease, collagen vascular disease, any systemic infection, patients with history of coronary angiography in the recent past, and those who u, Unwilling to give consent were excluded from the study. Patients suffering with acute coronary syndrome and those with chronic CAD were selected for the study Recent myocardial infarction is defined as an acute episode of infarction <1 months from the time of the investigation. 80 cases were selected for inclusion in the study based on clinical assessment and laboratory screening. An informed consent was obtained from each patient before inclusion in the study. Patient's age, gender, smoking history, body mass index, hypertension (systolic and diastolic blood pressures), heart rate, and medication history were recorded. Serum concentrations of total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, glucose, and creatinine using standard laboratory procedures were recorded. The severity of CAD was evaluated by the 0 to 3 vessel disease score and the Gensini score [10,11]. In the clinical 0 to 3 vessel disease scoring system ,arteries were as being involved if more than 50 % luminal diameter narrowing occurred, and the patients were defined as having 0-,1-,2-,3-vessel disease according to the number of involved vessels. The Gensini scoring system is used to estimate the severity of CAD according to angiographic findings

based on the evaluation of number of stenotic segments along with their respective degrees of luminal narrowing and localization within the coronary tree.

STATISTICAL ANALYSIS;

Data was analysed using Statistical Package for the Social Science (SPSS) Version 11.5 for Windows. Descriptive (frequencies, Percentages, Mean and Standard Deviation) and inferential Statistics were used to analyze the data. The inferential statistics used included Chi square, analysis of variance, correlation coefficient. Continues variables were presented as mean ± (SD). and compared through ANOVA test. Categorical variables by chi-square test and correlation coefficient was done where applicable. For all statistical tests P <0.05 was considered as statistically significant.

RESULTS

Males comprised 66 (82.50%) and female 14 (17.50%) of the total, Majority of them were males. The mean age of the whole group was 51.74 ± 9.01. Males had a lower mean age (51.41± 9.20) when compared to females (53.29 ± 8.21). The age group ranged from 28 to 73 years. Mean hs CRP level is slightly higher in female patients than in male patients, but the difference is statistically not significant. Significant correlation were found between hs-CRP and vessel Score. The scatter diagram shows that correlation coefficient was 0.760 which is highly significant (P < 0.01). Therefore there was linear positive correlation between hs-CRP and stenosis Score. Significant correlation were found between hs-CRP and vessel Score. The scatter diagram shows that correlation coefficient was 0.697 which is highly significant (P < 0.01). Therefore there was linear positive correlation between hs-CRP and vessel Score . Left anterior descending artery is the most commonly involved vessel in all three groups. Followed by circumflex and Right coronary artery. Mean hs CRP of 3.99 was seen in patients with previous myocardial infarction, 3.62 in patients who had UA/NSTEMI and in patients with chronic stable angina.

HsCRP levels were elevated in our study group irrespective of other traditional risk factors in acute coronary syndromes. Gensini scoring of CAD angiographic severity is in linear correlation to mean HsCRP levels. The Levels were correlating well with angiographic stenosis severity.Low HsCRP (<1 mg) is associated with less severe stenotic lesions.High HsCRP (>3 mg)is associated with severe stenotic lesions.Number of vessels involved in CAD patients correlates directly with CRP level groupings.Higher the HsCRP levels, more vessels involved. Those with Low HsCRP (<1 mg), had single vessel disease.Those with left main disease and its equivalents, triple vessel disease had very high mean HsCRP levels.

Table-1
High Sensitive C-reactive Protein (hs-CRP) distribution of the study Patients

hs-CRP	Number of Patients	Percentage
GROUP-I (< 1.0 mg / L)	19	23.75
GROUP –II (1.0 – 3.0 mg / L)	30	37.50
GROUP-III (> 3.0 mg / L)	31	38.75
TOTAL	80	100

Table-2
The distribution of Demographical characteristics of study sample

Variables		GROUP-I (N=19)		GROUP-II (N=30)		GROUP-III (N=31)		TOTAL	
		N	%	N	%	N	%	N	%
Sex	Male	16	84.20	25	83.30	25	80.60	66	82.50
	Female	3	15.80	5	16.70	6	19.40	14	17.50
Age Mean ±(SD)		48.74 ±10.84		49.77 ±7.63		55.48 ±7.93		51.74 ± 9.01	

Table - 3
SEX VERSUS MEAN CRP LEVEL

Hs-CRP	MALE (N=66)	FEMALE (N=14)
Mean	3.65	3.97
S Deviation	2.59	2.97
t-value	0.40	
Significant	0.68 (Not Significant)	

Table-4
Distribution of mean vessel and stenosis score

Variables	Group-I (N=19)	Group-II (N=30)	Group-III (N=31)	Significant ANOVA	
				F-value	Sign.
Vessel Score Mean ±(SD)	0.37 ± 0.83	1.40 ± 0.81	2.45± 0.85	37.84	P < 0.001
Stenosis Score Mean ±(SD)	4.00 ± 6.74	17.67 ± 11.40	45.13 ± 23.33	42.47	P < 0.001

Table-5
Correlation between hs-CRP score with Stenosis score and Vessel score

Variables	Stenosis Score	Vessel Score
hs-CRP level	0.760 **	0.697**

** Correlation is significant at P < 0.01

Table-6
hs-CRP Group with Diagnosis

	Group-I (N=19)		Group-II (N=30)		Group-III (N=31)		Total (N=80)	
	N	%	N	%	N	%	N	%
MI	9	47.4	18	60.0	17	54.8	44	55.0
UA/NSTEMI	4	21.1	4	13.3	4	12.9	12	15.0
CSA	6	25.0	8	26.7	10	32.3	24	30.0

Table-7
hs-CRP Group with vessel involvement.

Variables	Group-I (N=19)		Group-II (N=30)		Group-III (N=31)		Total (N=80)	
	N	%	N	%	N	%	N	%
Left Main	-	-	-	-	5	16.13	05	06.25
LAD	3	15.79	21	70.00	29	93.55	53	66.25
LCX	3	15.79	12	40.00	20	64.52	35	43.75
RCA	1	05.26	11	36.67	22	70.97	34	42.50

Limitations: Despite the statistically significant results of this study, larger cohorts are required in local settings to assess the relationship of hs-CRP levels with the severity of coronary atherosclerosis in local settings.

The coronary angiographic assessment is based upon luminal assessment and lacks plaque visualization. Intravascular ultrasound (IVUS) based assessment of coronary atherosclerotic burden in correlation with hs-CRP levels may be an area of interest for future investigation

DISCUSSION

Many population studies have demonstrated that hs CRP is a sensitive marker for inflammation and future cardiovascular risk[12,13].Marc S. Sabatin et al showed the population which included both patients with stable and patients with unstable angina, there were only 75 coronary events during the 2 years of follow-up, and excess risk was demonstrated only when hs-CRP levels were in the top quintile (>3.6 mg/L), with no evidence for a gradient of risk across the lower quintiles[14]. Tataru MC et al [15] showed correlation hs CRP and the severity of atherosclerosis in myocardial infarction patients with stable angina pectoris.

Zebrack et al, [16]showed hs CRP correlates with extent of coronary artery disease, Nyandak et al,[17] also showed correlation of hs CRP with extent of coronary artery disease. And hs CRP levels have a correlation with the disease burden in coronary artery disease patients.

Peppes et al,[18] study showed correlation between myocardial enzyme serum levels and markers of inflammation with severity of coronary artery disease and Gensini score .In contrast, using a large cohort of patients with stable CAD, it was able to prospectively

apply the CDC/AHA hs-CRP cut points and demonstrate that an elevated level of hs-CRP, even >1 mg/L, was associated with an increased risk of cardiovasculardeath, MI, or stroke.

The risk was consistent across all the elements of the composite end point and remained significant even after adjustment for elements of the Framingham Risk Score and other clinical and laboratory parameters. These data suggest that among patients with CAD, hs-CRP levels can be used to gain fundamental insight into which patients are, despite being asymptomatic at a given time and hence deemed clinically stable, in fact pathobiologically unstable and at higher risk for adverse cardiovascular events. However, an elevated hs-CRP does not appear to identify patients with stable CAD and preserved ejection fraction who derive particular benefit from ACE inhibition.

High sensitivity C-reactive protein (CRP), a marker of systemic in□ammation, has been evaluated as a risk predictor in subjects without known coronary artery disease (CAD), in those at risk of CAD and in patients with stable angina, unstable angina or acute myocardial infarction(MI). Even small elevations of CRP, within or just beyond the "normal" range (determined by high sensitivity CRP assay) have been found to strongly predict future cardiovascular events in almost all studies. However, these studies have not adjusted for plaque burden as assessed by coronary angiography .When adjustments for CAD have been made, they generally have been limited to adjustment for one -,two-or three-vessel disease and previous studies have shown a correlation between CRP and the presence of atherosclerosis.

CONCLUSION:

Higher hs-CRP levels were associated with higher stenosis score in CAD patients, which are consistent with the present study results. Hence, hs-CRP is a single cardiovascular risk factor and increases in hs CRP concentration within reference limit are associated with future cardiovascular events. Furthermore elevated level of C reactive protein can predict the coronary atherosclerotic disease burden

Conflict of interest: Nil

ACKNOWLEDGEMENTS

We sincerely acknowledge the individuals and their families participated in this study.

REFERENCES

1. Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure 1999;7:169-177.
2. Mohan V, Deepa R, Shanthi Rani S, Premlatha G. Pravelence of coronary artery disease and its relationship to lipids in a selected population of south India. The Chennai Urban Population Study (CUPS No. 5). J Am Col Cardiol 2001; 38: 682-7.
3. Biasucci LM. C-reactive protein and secondary prevention of coronary events. Clin Chim Acta. 2001; 311: 49–52.
4. Lindahl B, Toss H, Siegbahn A, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med. 2000; 343: 1139–1147.
5. Zebrack JS, Anderson JL, Maycock CA, et al. Usefulness of high-sensitivity C-reactive protein in predicting long-term risk of death or acute myocardial infarction in patients with unstable or stable angina pectoris or acute myocardial infarction. Am J Cardiol. 2002; 89: 145–149.
6. Zebrack JS, Muhlestein JB, Horne BD, et al. C-reactive protein and angiographic coronary artery disease: independent and additive predictors of risk in subjects with angina. J Am Coll Cardiol. 2002; 39: 632–637.
7. Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol. 1998; 31: 1460–1465.
8. Benamer H, Steg PG, Benessiano J, et al. Comparison of the prognostic value of C-reactive protein and troponin I in patients with unstable angina pectoris. Am J Cardiol. 1998; 82: 845–850.
9. Rebuzzi AG, Quaranta G, Liuzzo G, et al. Incremental prognostic value of serum levels of troponin T and C-reactive protein on admission in patients with unstable angina pectoris. Am J Cardiol. 1998; 82: 715–719.
10. Gensini GG. Coronary arteriography. Mount Kisco, New York: Futura Publishing Co, 1975.
11. David R, Sullivan MB, Thomas H et al. A new method of scoring coronary angiograms to reflect extent of coronary atherosclerosis and improve correlation with major risk factors. Am Heart J 1990; 119: 1262.
12. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of Creactive protein and coronary heart disease in the MRFIT. Am J Epidemiol 1996; 144: 537-47.
13. Nakakuki T, Ito M, Iwasaki H, Kureishi Y, Okamoto R, Moriki N, et al. Rho/Rho-kinase pathway contributes to C-reactive protein-induced plasminogen activator inhibitor-1 expression in endothelial cells. Arterioscler Thromb Vasc Biol 2005;25:2088-2093.
14. Schwedler SB, Amann K, Wernicke K, Krebs A, Nauck M, Wanner C, Potempa , et al. Native C-reactive protein increases whereas modified C-reactive protein reduces atherosclerosis in apolipoprotein E-knockout mice. Circulation 2005;112:1016-1023.
15 Zebrack JS, Muhlestein JB, Horne BD, Anderson JL. C-reactive protein and angiographic coronary artery disease: independent and additive predictors of risk in subjects with angina. J Am Coll Cardiol. 2002; 39: 632–637.
16 Vasileious Peppes, George Rammos, Efstathios Manios, Correlation between myocardial enzyme serum levels and markers of inflammation with severity of coronary artery disease and Gensini score, A hospital-based, prospective study in Greek patients, Clinical interventions in ageing 2008,3(4) 699-710.
17. Liu haihang,Zhao dong,Ma changssheng. Association of C reactive protein levels with the severity of coronary artery disease. Heart 2010,96 A 81.
18 Kartisis D ,Korovesis S,Giazitzoglou E, C reactive protein and angiographic characteristics of coronary lesions . Clin Chem. 2001; 47(5):882-886.