Original Article:

High sensitivity C-reactive protein levels across spectrum and severity of coronary artery disease

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ABSTRACT

Background: C-reactive protein (CRP) is an acute-phase reactant protein synthesized by the liver in response to acute stress in a wide range of acute and chronic inflammatory conditions. In healthy subjects and patients presenting with coronary artery disease (CAD), elevated levels of CRP has repeatedly been demonstrated to predict future cardiovascular events.

Methods: We measured high sensitivity C-reactive protein (hs-CRP) levels in 382 consecutive patients with CAD and 60 healthy controls by immunoturbidimetry method. Risk factors like hypertension, diabetes mellitus, dyslipidaemia, smoking, obesity and family history of premature CAD were assessed.

Results: The mean age of patients with CAD was 53.5±11.8 years (303 males) and that of control group was 50.83±8.07(28 males). The patient group had significant higher concentration of mean hs-CRP levels when compared with the healthy control group (1.8±1.9 mg/L vs 0.35±1.1 mg/L, $p<0.001$). The mean hs-CRP levels of unstable angina (USA) and myocardial infarction (MI) patients was higher than chronic stable angina (CSA) patients ($p<0.05$). Based on the disease severity, we found a significantly higher hs-CRP levels in patients of triple vessel disease when compared to patients with single vessel disease ($p=0.01$).

Conclusions: Elevated serum hs-CRP levels provide a useful marker for cardiovascular risk which, when combined with traditional risk factors, may help improve global risk prediction. Our study showed a significant contribution of hs-CRP to coronary risk prediction with better discrimination.

Key words: High sensitivity C-reactive protein, Chronic stable angina, Atherosclerosis, Dyslipidaemia.

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INTRODUCTION

C-reactive protein (CRP), named for its capacity to precipitate the somatic C-polysaccharide of Streptococcus pneumonia, was the first acute-phase protein to be described and is considered to be an exquisitely sensitive systemic marker of inflammation and tissue damage.[1] Inflammation plays a major role in all stages of atherosclerosis, from lesion initiation to plaque rupture and ultimately the clinical thrombotic complications.[2] Elevated levels of high sensitivity C-reactive protein (hs-CRP) in healthy patients have been found to be predictive of a first cardiac event and is useful in identifying patients at increased risk for a cardiac event.[3,4] Being a sensitive marker of inflammation, CRP responds rapidly to various pro-inflammatory stimuli, is elevated during atherogenesis and may serve as a marker of ongoing atherosclerosis. Furthermore, CRP activates complement after binding to oxidized low-density lipoprotein (LDL), and mediates the uptake of LDL-cholesterol (LDL-C) by macrophages.[5] Role of inflammation in the pathogenesis of atherosclerosis especially the associations between CRP with cardiovascular risk factors and disease risk have gained much attention in the recent past.[6] Some studies have shown that serum hs-CRP measurements are predictive of cardiovascular ischaemia and death in patient populations with angina or acute coronary syndromes (ACS).[7] There is evidence that hs-CRP, a leading inflammatory biomarker for clinical application, is independently associated with the risk of in-

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cidence or recurring cardiovascular events regardless of the lipid levels.[8]

MATERIAL AND METHODS

Study population

We recruited 382 consecutive patients with CAD, admitted under care of the Department of Cardiology, Sri Venkateswara Institute of Medical Sciences, Tirupati, India, from August 2004 to August 2005. The study included patients attending out-patient service as well as admissions into intensive coronary care unit (ICCU). The patient group included the entire spectrum of CAD, ie., chronic stable angina (CSA), unstable angina (USA) and myocardial infarction (MI), ST elevation myocardial infarction(STEMI) and non-ST elevation myocardial infarction (NSTEMI). The diagnosis of CAD was evidenced by electrocardiogram (ECG) abnormalities, positive exercise testing [treadmill test (TMT), perfusion scan (Tc-MIBI)], elevated creatine phosphokinase (CPK), and its isoenzyme CPK-MB and coronary angiography (CAG). Patients with other systemic illnesses where CRP is elevated (infections, chronic inflammatory diseases like rheumatoid arthritis etc.), patients with malignancies, who had recent surgery or trauma, who were on anti-inflammatory drugs, anti-hyperlipidaemic agents and glitazones and women on oral contraceptive pills were excluded from this study. Sixty healthy individuals were recruited into the control group. This study was approved by the Institutional Ethical Committee.

Baseline assessment

Baseline assessment in all patients included a detailed history, physical examination and cardiovascular examination. Risk factors like diabetes mellitus, hypertension, smoking, obesity and family history of premature CAD were assessed. Earlier history of dyslipidaemia and history of receiving statin therapy were also enquired. Obesity was defined as body mass index (BMI) greater than 25 Kg/m^2 in patients who underwent diagnostic CAG.[9]

Laboratory and other investigative measurements

All patients underwent routine investigations like haemoglobin, total white blood cell count, erythrocyte sedimentation rate, ECG and chest radiograph. Fasting serum lipid profile [total cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides] was done in all patients by using commercially available kits on autoanalyzer (Synchron CX9 from Beckman USA). Low density lipoprotein (LDL) cholesterol values were calculated using the Friedewald formula.[10] Echocardiography was done in all patients and controls using Sonos-7500 (Philips, Netherlands) machine. A subset of patients (n=221) underwent diagnostic CAG. Serum samples for hs-CRP estimation were assayed by Immunoturbidimetry method (Tulip diagnostics, India).

Statistical analysis

All continuous variables were expressed as mean and standard deviation; whereas categorical variables were expressed as numbers with percentages. Continuous variables were compared using Students t-test and one-way analysis of variance (one-way ANOVA). Relationship between dependent variable CAD and independent variables was studied using regression analysis. All computation and statistical analysis were done using SPSS version 13.0, SPSS Inc. Chicago, USA.

RESULTS

The mean age of patients with CAD was 53.5±11.8 years (303 males). The mean age of control group was 50.8±8.1 years (28 males). Table 1 shows the clinical characteristics of the study population and control subjects. The patients with CAD had significantly higher hs-CRP levels when compared with the healthy control group (1.8±1.9 mg/L vs 0.35±1.1 mg/L; $p<0.001$). The mean hs-CRP levels in patients with CSA, USA and MI are shown in Table 2. The hs-CRP levels were significantly higher in USA and MI subgroups when com-

pared to CSA subgroup ($p<0.05$). We found a significantly higher hs-CRP levels in patients with triple vessel disease when compared to patients having single vessel disease (1.9±2.4 mg/L vs 1.4±1.5 mg/L; p=0.01) (Table 3). In the present study also higher levels of hs-CRP were in the middle aged asymptomatic healthy controls (0.7±0.9 in mg/L control group;1.8±1.7 mg/L in patient group; age 31-40 years) than young subjects (0.2±0.2 mg/L in control group;1.5±1.1 mg/L in patient group; age 20-30 years). Regression analysis showed no association between mean hs-CRP levels and serum lipid levels.

When the patients were stratified according to cardiovascular risk based on the hs-CRP levels, there were 40% patients in lowest risk group (hs-CRP range 0.1-0.7 mg/L), 15% patients in moderate risk group (hs-CRP range: 1.2-1.9 mg/L) and 13% persons in highest risk group (hs-CRP range 3.9-15 mg/L) (Table 4).

Table 1: Clinical characteristics of the study population and control group

Risk factor	Patients (n=382)	Controls (n=60)	p-value
Age (Years)	53.5±11.8	50.83±8.07	NS
Males [No. (%)]	303 (79%)	28 (47%)	NS
Females [No. (%)]	79 (21%)	32 (53%)	NS
Hypertension [No. (%)]	192 (50%)	16 (26%)	NS
Diabetes mellitus [No. (%)]	155 (41%)	11 (18%)	NS
Smoking [No. (%)]	100 (26%)	09 (15%)	NS
Haemoglobin (g/dL)	12.67±7.34	–	NS
Total cell count (mm^3)	11634.68±9055.12	–	NS
Total cholesterol (mg/dL)	188.62±47.73	150.28±30.13	NS
LDL cholesterol (mg/dL)	115.94±83.97	103.19±28.60	NS
HDL cholesterol (mg/dL)	38.36±5.85	41.33±6.02	NS
Triglycerides (mg/dL)	156.78±80.08	120.74±39.86	NS
VLDLC (mg/dL)	28.75±17.55	–	NS
LVEF (%)	48.30±13.69	–	NS
hs-CRP (mg/L)	1.8±1.9	0.35±1.1*	0.001

Data are expressed as mean and standard deviation for continuous variables
*$p<0.001$
LDL = low density lipoprotein; HDL = high density lipoprotein; VLDLC = very low density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; hs-CRP = high sensitivity C-reactive protein

Table 2: Mean hs-CRP levels based on type of disease in patients with CAD (n = 382)

Disease severity	No. (%)	Mean hs-CRP (mg/L)*	p-value
CSA	102 (27)	1.4±1.3	
USA	74 (19)	2.0±2.0	
MI	206 (54)	2.0±2.0	†

*Data are expressed as mean and standard deviation

†mean hs-CRP levels were significantly lower in CSA group when compared with USA and MI groups ($p<0.05$)
CAD = coronary artery disease; CSA = chronic stable angina; USA = unstable angina; MI = myocardial infarction; hs-CRP = high sensitivity C-reactive protein

Table 3: Mean hs-CRP levels based on vessel disease severity in 221 patients who underwent CAG

Vessel severity	No. (%)	Mean hs-CRP (mg/L)*
Normal coronaries	35 (16)	1.5±1.9
SVD	92 (42)	1.4±1.5
2VD	34 (15)	1.5±1.5
TVD	60 (27)	1.9±2.4†

* data are expressed as mean ± standard deviation
† significantly higher when compared with SVD (p=0.01)
CAG = coronary angiography; SVD = single vessel disease; 2VD = two vessel disease; TVD = triple vessel disease

Table 4: hs-CRP levels and risk distribution in patients with CAD

hs-CRP (mg/L)	Risk group	Distribution(%)
0.1-0.7	Lowest	40
0.8-1.1	Low	10
1.2-1.9	Moderate	15
2.0-3.8	High	22
3.9-15	Highest	13

CAD = coronary artery disease

DISCUSSION

Available evidence in the literature shows that higher levels of hs-CRP are observed in CAD patients than normal subjects.[11-13] In the present study also higher levels of hs-CRP were observed in patients when compared to controls (p<0.001). When comparing the values in three groups of CAD patients, significantly higher levels were observed in patients with USA and MI when compared to patients of CSA (p<0.05). Our findings are in agreement with the findings of the Chennai study.[12] The hs-CRP levels in the present study are lower than the observations reported in other studies.[14,15] In this study we observed significantly higher hs-CRP levels in triple vessel disease than in single vessel disease (1.9±2.4 Vs 1.4±1.5; p=0.01). In this study hs-CRP levels were not influenced by the lipid profile (total cholesterol, HDLC, LDLC and triglycerides) which showed no association in regression analysis. Earlier study by Achari et al[16] showed higher levels of TC and decreased HDLC in patients than controls. Present study showed no statistically significant difference in mean hs-CRP levels in patients with normal and elevated TC, LDLC and triglycerides. However, patients with low HDLC have higher mean hs-CRP levels when compared to patients with higher HDLC (p=0.01).

Serum hs-CRP levels have been shown to predict MI, stroke, peripheral arterial disease and sudden cardiac death.[17,18] In the present study hs-CRP levels showed positive association with CAD in univariate logistic regression analysis (OR: 2.4; 95% CI: 2.4-2.74; p<0.01). In a Japanese study[19] lower levels of hs-CRP were observed in young adults (19-27 years) than middle age group (40-60 years). Our observations are also similar to this study.

Elevated levels of hs-CRP in patients when compared to controls, significant difference in the levels of hs-CRP in acute coronary syndromes, positive association with CAD and absence of association of hs-CRP with lipid parameters in our study, suggest that hs-CRP may act as a risk factor independent of lipid levels in predicting the risk of CAD. Our findings also support the observations of Ridker et al[20] who showed that reduced levels of hs-CRP results in decreased incidence of cardiovascular events. Thus our findings suggest that higher levels of hs-CRP are independently associated

with an increased risk of CAD.

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