Original article

High-sensitivity C-reactive protein in Sri Lankan males with coronary artery disease

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Abstract:

Objectives: Evidence suggests that inflammation and dyslipideamia play a key role in the pathogenesis of coronary artery disease (CAD). High sensitivity C-reactive protein (hs-CRP) is a sensitive marker of inflammation. We attempted to evaluate the contribution of dyslipidaemia and inflammation in CAD. ***Materials and methods***: Three hundred and nine males (103 with myocardial infarction - MI, 103 with established CAD, 103 healthy controls) were studied. The serum hs-CRP, lipids and plasma glucose were determined. ***Results***: Baseline mean hs-CRP levels in patients with established CAD and MI were significantly higher compared to controls (3.4 ± 1.62 VS. 1.70 ± 0.60 mg/L, $p = 0.001$) (3.7 ± 0.65 VS. 1.70 ± 0.60 mg/L, $p = 0.001$). A significant negative correlation observed between hs-CRP and HDL-Ch ($r = -0.359$, $p = 0.001$). ***Conclusion***: Inflammation (which was reflected by elevated hs-CRP) and dyslipidamia were associated with coronary artery disease.

Key words: Coronary artery disease; dyslipidaemia; high- sensitivity-C-reactive protein.

Bangladesh Journal of Medical Science Vol. 15 No. 01 January'16. Page : 44-50

Introduction:

Atherosclerosis is clearly multi-factorial, but the role of inflammatory processes in coronary artery disease has been of great interest in recent years. The pathophysiology of atherosclerosis has been linked to an inflammatory reaction as a response to injury, characterized by the expression of adhesion molecules in the endothelium, subsequent uptake of blood monocytes and conversion to macrophages, triggering of cytokine activity, and activation of T lymphocytes[1].

Elevated markers of inflammatory activity are associated with an increased risk of future cardiovascular events in healthy individuals[2,3] and in patients with stable[4] and unstable coronary artery disease[5,6]. High-sensitivity C-reactive protein (hs-CRP), proposed as a new coronary risk marker, may reflect either an acute phase reaction or the level of chronic inflammation. High-sensitivity C-reactive protein has attracted increasing attention in recent years following epidemiologic studies consistently showing hs-CRP as an independent predictor associated with risk of future cardiovascular events in those who are at risk[7]. In clinical practice, the inflammatory biomarker in widest use is hs-CRP. When interpreted within the context of usual risk, levels of hs-CRP < 1, 1 to 3, and > 3 mg/L denote lower, average, and higher relative risk for vascular events[8].

Accumulating evidence indicates the link between inflammation, dyslipidaemia and atherosclerosis[9-13]. The lipid changes that are observed are not only quantitative but also qualitative, with changes in the composition of lipoproteins during inflammation[14-17]. The evidence that shows the association between coronary artery disease, cardiovascular risk factors and hs-CRP is scarce especially in the local setting. This study attempted to evaluate the contribution of dyslipidaemia and inflammation in coronary artery disease.

Materials and Methods:

Selection of study subjects

Group 1 comprised of 103 male patients (age range of 30-70 yrs) admitted consecutively to Coronary

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Care Unit, Teaching hospital Karapitiya, Sri Lanka with acute STEMI (n = 103). The diagnosis of STEMI was made on the basis of typical history and electrocardiographic changes and all recruited patients fulfilled the American College of Cardiology/American Heart Association criteria for acute coronary syndrome[18].

Group 2 comprised of 103 male patients (age range of 30-70 yrs) with angiographically- proven established CAD awaiting CABG.

Group 3 comprised of 103 controls, selected from patients awaiting minor surgery without clinically manifested coronary artery disease. Those with abnormal electrocardiograms were not considered for recruitment as controls.

The common exclusion criteria were as follows: history of recent surgery or major trauma (within 3 months) or history of acute coronary syndrome in the past 3 months, previous coronary artery bypass graft (CABG), malignancy, chronic inflammatory disorders, current acute severe infections (CRP level more than 10 mg/dL), dementia or any structural damage to the central nervous system, renal dysfunction (was defined as serum creatinine concentration more than 2 mg/dL (177 mmol/L), chronic liver disease and alcohol dependency based on the CAGE[19].

This clinical protocol was approved by the Ethical Review Committee of Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka and conducted according to the ethical guidelines outlined in the Declaration of Helsinki.

An interviewer-administered questionnaire was used to collect the following information: socio-demographic data, risk factors such as hypertension, diabetes mellitus, cigarettes smoking, hyperlipideamia, family history of coronary heart disease, previous myocardial infarction and medications. Weight, height, waist circumference, hip circumference, systolic and diastolic blood pressure (mean of 3 consecutive measurements) were measured. The same investigator performed all measurements using the same instruments.

Patients with STEMI (Group 1) who were admitted within a mean of 4.3 hours from the onset of symptoms were recruited and a sample of blood was obtained on-admission. Patients with established CAD (Group 2) and controls (Group 3); blood samples were obtained in the morning after an overnight fast.

Fasting plasma glucose, serum total cholesterol (TCh), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-Ch) were estimated by enzyme based colorimetry method using a commercial kit (ProDia International, UAE). LDL-cholesterol level was calculated using Friedewald formula except when TG exceeds 4.5 mmol/L[20].

In the STEMI group, the serum level of cardiac troponin I was measured using a test kit based on enyme-labeled chemiluminescent immunometric assay (IMMULITE 1000 Troponin I). Serum hs-CRP was measured by commercially available test kit based on turbidimetry (DIAgAM, Rue du Parc Industriel, 7822, GHISLENGHIEN Belgium). Assays were performed blind with respect to information of the subject.

Data were analyzed using appropriate statistical tests. Categorical baseline data were displayed as percentages and frequencies. Categorical data were analyzed using the Chi-squared test or Fisher's exact test. Numerical data were examined for normality and presented as mean $\pm$ SD. Continuous variables were presented as mean $\pm$ SD. Groups were compared by two sample *t* – test. Correlations were tested by Pearson correlation coefficient. Adjusted means of lipid levels, plasma glucose hs-CRP were calculated using multiple regressions. For lipids and for plasma glucose; age, BMI and presence of diabetes mellitus were used as clinical covariates. For hs-CRP; age, BMI, smoking, presence of diabetes mellitus, statin and aspirin use were considered as confounders. Differences were considered to be significant if the null hypothesis could be rejected with $> 95\%$ confidence, when p values < 0.05.

Results:

Mean ages of the established coronary artery diseased group and the control group were significantly different ($p = 0.001$) and mean ages of the STEMI group and the established CAD group were also significantly different ($p = 0.010$), but the mean ages of the STEMI group and the control group were not significantly different ($p = 0.201$). It reflected that patients with established CAD awaiting CABG were relatively older than the patients with first STEMI. Basic characteristics of the three groups were presented in Table 1 and 2.

Body mass index of patients with established CAD was higher and significantly different from control group ($p = 0.001$) and the STEMI group ($p = 0.001$), but BMI of the STEMI group was not significantly different from control group ($p = 0.55$). Mean waist circumference of the established CAD group was significantly different from both

Table 1. Comparison of basic characteristic between the STEMI group and the control group

Characteristic	Group 1 STEMI (n = 103)	Group 3 Controls (n = 103)	*p*
Age (years)	54 ± 8	52 ± 11	0.201
BMI (kgm^{-2})	21.2 ± 3	22.4 ± 5	0.055
Waist circumference (cm)	76.9 ± 10	75.9 ± 10	0.462
Waist/hip ratio	0.91 ±.06	0.91 ± 0.07	0.997
SBP mmHg	136 ±26	125 ±13	0.001
DBP mmHg	87 ± 18	79 ± 8	0.001
Diabetes mellitus	13.6 %	Not present	-
Hypertension	19.4 %	Not present	-
Cerebrovascular disease	1.9 %	Not present	-
Smoking	57.3 %	Not present	-
Statin treatment	4.8 %	Not used	-
hs-CRP (mg/L)	3.7 ± 0.65	1.7 ± 0.60	0.001
TGs (mmol/L)	2.1 ± 1.07	1.5± 0.8	0.001
TCh (mmol/L)	6.1 ± 2.3	5.2 ± 1.6	0.001
HDL-Ch (mmol/L)	1.1 ± 0.52	1.4 ± 0.6	0.001
LDL- Ch (mmol/L)	4.5 ± 2.3	3.1± 0.5	0.001
PG (mmol/L)	6 ± 2.0	5.1± 0.6	0.001

Data expressed as mean ± SD or frequencies/percentages. Two groups were compared using the two sample *t*- tests. hs-CRP = highly sensitive-C reactive protein, TGs = Triglycerides, TCh = Total cholesterol, HDL-Ch = High-density lipoprotein cholesterol, LDL-Ch = Low density lipoprotein cholesterol, PG = Plasma glucose, STEMI = ST- elevation myocardial infarction.

STEMI group and the control group ($p = 0.001$), while mean waist circumference of the STEMI group showed no difference from the controls ($p = 0.462$). Mean waist to hip ratio (W/H ratio) of the established CAD group was significantly different from STEMI group and the control group ($p = 0.001$), but W/H ratio of STEMI group was not significantly different from the control group ($p = 0.997$). Therefore, as reflected by the anthropometric indices, prevalence of obesity (BMI > 30 kg/m^2) seemed to be more in the established CAD group (3.9%) rather than the STEMI group 2 (1.9 %). Furthermore, the prevalence of traditional risk factors was higher in the established CAD group, although the prevalence of smoking showed no difference between the two diseased groups ($p = 0.270$).

Baseline mean hs-CRP concentration in established CAD patients were significantly higher compared to control group (3.4 ± 1.62 vs. 1.7 ± 0.60 mg/L, $p = 0.001$). A significant difference (3.70 ± 0.65 vs 1.70 ± 0.60 mg/L, $p = 0.001$) was observed between on-admission (baseline) serum hs-CRP in patients with STEMI and mean hs-CRP level in the control group. However, baseline mean hs-CRP concentrations were not significantly different between the established CAD group and the STEMI group (3.4 ± 1.62 vs. 3.70 ± 0.65 mg/L, $p = 0.058$). Serum lipids (TCh, TGs and LDL-Ch) and plasma glucose were significantly higher in both cases groups compared to controls, while HDL-Ch was significantly higher in controls compared to cases (all $p < 0.05$).

When correlations between hs-CRP and other measurements were examined age, waist, hip, TCh, TGs, LDL-Ch showed significance positive correlations while, HDL-Ch showed significance negative correlation. Body mass index, plasma glucose and blood pressure did not exhibit significant relationships. This is shown in Table 3.

Discussion

Our study showed that hs-CRP levels both in established CAD group and the STEMI group were significantly higher compared to controls. There are similar reports supporting our study showing relatively elevated hs-CRP in patients with CAD,

Table 2. Comparison of basic characteristic between the established CAD group and the control group

Characteristic	Group 2 Established CAD (n = 103)	Group 3 Controls (n = 103)	*p*
Age (years)	57 ± 8	52 ± 11	0.001
BMI (kgm^{-2})	23.9 ±3	22.4 ± 5	0.001
Waist circumference (cm)	87.9 ± 7	75.9 ± 10	0.001
Waist/hip ratio	0.94 ± 0.05	0.91 ± 0.07	0.001
SBP mmHg	120 ±14	125 ±13	0.01
DBP mmHg	71 ± 8	79 ± 8	0.001
Diabetes mellitus	35.9 %	Not present	-
Hypertension	46.6 %	Not present	-
Cerebrovascular disease	17.5 %	Not present	-
Smoking	31 %	Not present	-
Statin treatment	95.1 %	Not present	-
hs-CRP (mg/L)	3.4 ± 1.62	1.7 ± 0.60	0.001
TGs (mmol/L)	2.5 ± 1.0	1.5± 0.8	0.001
TCh (mmol/L)	5.9 ± 2.8	5.2 ± 1.6	0.022
HDL-Ch (mmol/L)	1.1± 0.5	1.4 ± 0.6	0.001
LDL- Ch (mmol/L)	3.9 ± 1.2	3.1± 0.5	0.001
PG (mmol/L)	5.5 ± 1.4	5.1± 0.6	0.007

Data expressed as mean ± SD or frequencies/percentages. Two groups were compared using the two sample *t*- tests. hs-CRP = highly sensitive-C reactive protein, TGs = Triglycerides, TCh = Total cholesterol, HDL-Ch = High-density lipoprotein cholesterol, LDL-Ch = Low density lipoprotein cholesterol, PG = Plasma glucose, CAD = Coronary artery disease

Table 3. Relationship between serum hs-CRP levels and other measurements

Measurements	hs-CRP	Measurements	hs-CRP
Age	0.192 (0.001)	DBP mmHg	0.030 (0.599)
BMI	-0.003(0.954)	Triglycerides	0.218 (0.001)
Waist circumference	0.138 (0.015)	Total cholesterol	0.164(0.004)
Hip circumference	0.160 (0.005)	HDL- cholesterol	-0.359(0.001)
Waist/hip ratio	0.044(0.439)	LDL –cholesterol	0.288 (0.001)
SBP mmHg	0.090 (0.114)	Plasma glucose	0.093(0.103)

BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HDL-Ch = High-density lipoprotein cholesterol, LDL-Ch = Low density lipoprotein cholesterol, PG = Plasma glucose, hs-CRP = high sensitive C-reactive protein. Number outside the parentheses represents value of correlation coefficient; *p* - values for correlation coefficient are shown in the parentheses. Correlations were tested by Pearson correlation coefficient

suggesting the possible role of inflammation in atherosclerosis[21,22], meanwhile there is evidence showing no significant difference of hs-CRP concentration between cases and controls[23]. Furthermore, with the recognition of atherosclerosis as an inflammatory process, hs-CRP has been evaluated as a potential tool for prediction of the risk of coronary events[7, 24, 25].

Our data did not demonstrate significantly elevated baseline (on admission) hs-CRP levels in patients with STEMI compared to patients with established coronary artery disease, proving that baseline hs-CRP levels may fail to differentiate patients with established CAD from patients with acute coronary syndromes. Our data do not support previous reports, which found significantly higher

baseline levels of hs-CRP in patients with UA or AMI compared with levels in patients with stable CAD[26-28].

The chronic inflammatory process in established atherosclerotic disease and in acute inflammation during the initial period of plaque instability with only a few inflammatory cells in ACS induce CRP production that reaches levels not high enough to detect statistically significant differences between the two groups. Therefore baseline hs-CRP may not be suitable for distinguishing between patients with stable CAD and patients with acute coronary syndromes[28].

Atherosclerosis is a progressive disease and is increasingly being recognized as a complex phenomenon involving the interaction of several mechanisms: dyslipidaemia, inflammation, thrombosis and other dysfunctional metabolic syndromes. Our study revealed significantly higher serum levels of total cholesterol, triglycerides, LDL-cholesterol in cases compared to controls and it was demonstrated that there was a significant negative correlation between hs-CRP and HDL-Ch, while hs-CRP showed significant positive correlations with other lipid measurements in study subjects. Therefore the present study illustrates the interplay between inflammation (indicated by elevated hs-CRP) and dyslipidaemia. These findings are in line with the recent literature[9, 10]. However, still inconsistencies exists among the studies. Some studies showed a positive correlation between CRP with LDL-cholesterol and serum total cholesterol in patients with coronary artery disease, while no significant correlation of CRP was seen with high density lipoprotein and triglyceride[11]. In contrast, absence of correlation between plasma levels of CRP and serum total cholesterol and high-density lipoprotein cholesterol has also been reported[12].

One report showed significantly higher levels of inflammatory mediators such as CRP and TNF-□ in the North Indian male patients with acute myocardial infarction, compared with control subjects, and a highly significant positive correlation between lipoprotein (a) and inflammatory markers, clearly pointing to a role of inflammation and dyslipidaemia in the pathogenesis of CAD in the atherosclerosis-prone North Indian population[9].

It is evident that during inflammation, the lipid changes that are observed are not only quantitative but also qualitative, with changes in the composition of lipoproteins. Therefore, the proportion of triglycerides, phospholipids and cholesterol is increased in VLDL, IDL and LDL particles, whereas the proportion of cholesterol and triglycerides decreases in HDL particles[14]. Inflammation is associated not only with a decrease in HDL cholesterol levels but also with a change in the composition. HDL-cholesterol which circulates during inflammation are depleted in cholesterol esters but enriched in free cholesterol, triglyceride and sphingolipids[15]. C-reactive protein plays a major role in regulating lipoprotein metabolism and it promotes uptake of native LDL-cholesterol[16]. Moreover another study importantly demonstrated a positive correlation between oxidized-LDL-cholesterol and CRP levels[17].

The present study showed significant positive correlation between hs-CRP and waist and hip circumferences, although no significant correlation was found with body mass index. Obesity is a widespread and growing problem and C-reactive protein is correlated with obesity measurements[29]. There is evidence to prove the significant association between hs-CRP, and anthropometric variables in CAD patients, however not as significant as previously described in healthy patients[30, 31].

Conclusions:

In conclusion, serum hs-CRP levels were high both in patients with established CAD and ST- elevation myocardial infarction compared to controls. Baseline (on admission) hs-CRP levels in patients with STEMI were not elevated compared to patients with established coronary artery disease. A significant negative correlation observed between hs-CRP and HDL-Ch in, while significant positive correlations were seen between hs-CRP and other lipid measurements. A significant positive correlation existed between hs-CRP and waist and hip circumferences. Therefore higher levels of hs-CRP appear to be promoting dyslipideamia associated with obesity and it is a marker of atherogenic milieu reflecting the chronic inflammatory process involved.

Accumulating literature indicates that information gained the link between inflammation, dyslipidaemia and atherosclerosis, which is of significant clinical utility. New insights into the interplay between dyslipidaemia and inflammation in atherosclerosis may aid in identifying innovative therapeutic strategies to improve outcomes of individuals at risk for atherosclerosis. However, our study is a cross-sectional, case-control study and it is difficult to comment on the causality and need further investigations.

Conflict of interest:

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgement:

We wish to acknowledge the University Grants Commission, Sri Lanka for the financial assistance provided for the project (Grant No: UGC/ICD/CRF/2009/2/47) and Mrs. DABN Amerasekara, statistician (Applied Statistic Association, Sri Lanka), senior lecturer, Department of Crop Science, Faculty of Agriculture, University of Ruhuna, Sri Lanka for the statistical advice provided.

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