Association of Coronary Heart Disease and CRP – as a Noble Marker of Inflammation - A Case Control Study

Narayan Chandra Sarkar1, Piyabi Sarkar2*, Pubali Sarkar3, Suranjita Das4

Abstract

Background: Attention has increasingly turned towards the role of factors, such as inflammation in the development of atherosclerosis and CHD. C-reactive protein (CRP) has emerged as one of the most important novel inflammatory marker. Subsequent risk modification and treatment strategies of CHD keeping on pointer towards inflammation may be the appropriate approach.

Aim: The aim of this study was to determine the association of CHD with CRP, a sensitive marker of inflammation.

Material and Methods: This is a case control study amongst 300 subjects (150 cases and 150 controls), conducted in the Department of Cardiology at Sri Aurobindo Medical College and P.G Institute, Indore, M.P. Subjects with definite diagnosis of CHD established by coronary angiography (CAG) was taken as cases, subjects matched with age, gender with no conventional risk factor and past history of CHD from the relatives and accompanying persons were enlisted as controls.

Results: Estimation of CRP reveals ≥0.6 mg/dl in 88 (58.7%) subjects out of 150, compared to 26 (17.3%) control subjects out of 150 which is statistically significant (p value<0.0001) (OR=6.7).

Conclusion: CRP as a noble marker of inflammation was significantly higher in subjects of CHD and thus supported adequately the hypothesis of an activation of inflammatory cascade for coronary atheromatous plaque formation and causation of CHD.

Introduction

Coronary heart disease (CHD) is one of the leading causes of death and disease burden throughout the world. Communicable diseases have been concurred by various preventive measures such as adequate public health care, immunization and invention of various antibiotics but metabolic diseases especially CHD is the major concern which is yet to be concurred adequately and uniformly worldwide. Current global death toll due to CHD is 17.3 million per year.1,2

It is apprehended that death toll will be mounted to 33.6 million by 2030 of which 20% deaths will be shared by high income group countries, 8% by upper middle income group of countries, 37% by lower middle income countries and 35% by low income group of countries including India. In India CHD is in the form of epidemic.3

There are 30 million CHD patients in India in the term of absolute number. Acute myocardial infarction (AMI) death toll is 31.7% all death and enhancement of death rate from 2% in the year 1970 to 4.5% in the year 2000.CHD is a major health and economical burden in the developing country like India. According to the recent epidemiological studies, it is apprehended that Indian subcontinent will have to bear more than half of the burden of risk and eventuality of CHD in the coming days.3,4

During the past decades much knowledge has been achieved regarding the risk factors and pathophysiology of CHD but exact mechanism underlying development of CHD still remains to be fully evaluated. Multiple risk factors such as hypertension, diabetes mellitus (Type II DM), dyslipidemia, tobacco smoking, obesity and physical inactivity have been identified. However despite identification of risk factors, about half of all events of CHD reported to occur in apparently healthy individuals who have a few or none of the traditional risk factors. Now attention has been increasingly turned to the roll of other factors such as inflammation, in the development of atherosclerosis and CHD.5,6

Atherosclerotic plaque refers to a variable combination of changes of the intima of coronary arteries consisting of a focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue, calcium deposits and associated medial changes. Coronary atherosclerotic plaque formation is the underlying pathology responsible for CHD which is considered as an inflammatory disease. Recent studies suggested that the atherosclerotic process is characterized by low grade inflammation altering the endothelium of coronary arteries and is manifested with an increased level of marker of inflammation such as CRP and other cytokines.

The atheromatous plaque fissuring and rupture is the primary event of AMI.8 Plaque disruption exposes the underlying sub endothelial matrix to formed elements of circulating blood leading to activation of platelets, thrombin generation and clot formation. This process of blockage of coronary
artery deprived the heart muscle of oxygen and nutrients subsequently AMI.6

During the last 15 years compelling experimental and clinical evidence have demonstrated that both systemic and local inflammation might play a prominent role in the pathogenesis of atherosclerosis and it’s clinical consequence.7

Among the inflammatory biomarkers, CRP is an important bio marker of inflammatory process which has been considered as a causal factor and predictor of CHD in many studies. CRP levels are stable over long periods and have no diurnal variation and can be measured accurately. CRP reduces the expression of nitric oxide (NO) synthetase and prostacyclin synthetase and binds low density Lipoprotein (LDL-C) and promotes its uptake by macrophages, a key process in the genesis of atherosclerosis. It also regulates the expression of adhesion molecule on endothelial cells. All these phenomena are associated with atheromatous plaque formation.

Material and Methods

This was a case control study to determine the possible association of CRP a noble marker of inflammation in the pathophysiology of atheromatous plaque formation in the coronary arteries leading to the causation of CHD. This study was conducted at Department of Cardiology, Sri Aurobindo Medical College and P.G. institute, Indore, M.P from June 2013-December 2016. This is a tertiary care hospital which drains patient from urban, and rural areas of adjoining districts of M.P from all classes of socio economical section of the society.

A round figure of 300 patients were enlisted for this study (150 cases and 150 controls). Subject aged 40-60 years followed by 46 (30.7%) cases were there in the 51-60 years and 36 (24%) cases in the 61 years and above category. Among the controls 72 (48%) subjects were in the age group of 51-60 years and 35 (23.3%) cases were there in the 61 years and above category.

Table 1: Distribution of study subjects according to age

<table>
<thead>
<tr>
<th>Age</th>
<th>Case (n %)</th>
<th>Control (n %)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50 years</td>
<td>69 (46%)</td>
<td>72 (48%)</td>
<td>0.878</td>
</tr>
<tr>
<td>51-60 years</td>
<td>46 (30.7%)</td>
<td>42 (28%)</td>
<td></td>
</tr>
<tr>
<td>61 years and above</td>
<td>35 (23.3%)</td>
<td>36 (24%)</td>
<td></td>
</tr>
<tr>
<td>Total (N %)</td>
<td>150 (100%)</td>
<td>150 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

P value=0.878, Chi square value=0.2597

Table 2: Distribution of study subjects according to gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Case (n %)</th>
<th>Control (n %)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>111 (74.0%)</td>
<td>112 (74.2%)</td>
<td>0.895</td>
</tr>
<tr>
<td>Female</td>
<td>39 (26.0%)</td>
<td>38 (25.3%)</td>
<td></td>
</tr>
<tr>
<td>Total (N %)</td>
<td>150 (100%)</td>
<td>150 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

P value=0.895, chi square value=0.0174

Age, gender and socio economical status were taken as controls. Patients having Type 2 DM, Hypertension, Rheumatoid arthritis, dyslipidemia, asthma, acute infections, co-morbid diseases and malignancy were excluded from the study. Blood samples were collected from the study subjects for both cases and control to estimate CRP, lipid profile and blood sugar level.

The CRP values were recorded as per manufacturer’s guidelines – Quantia (CRP) by Tulip diagnostics (p) ltd. The CRP measured value ≥0.6 mg/dl was considered as significant.

Ethical approval for the study was obtained from Institutional review board of Sri Aurobindo Institute of Medical Sciences, Indore (M.P). Permission was obtained from Department of Cardiology, Sri Aurobindo Institute of Medical Sciences, Indore (M.P). Written informed consent was obtained from all the subjects before conducting the study.

Results

Table 1 shows a total of 300 subjects were examined among which 69 (46%) cases were in the age group of 40-50 years followed by 46 (30.7%) cases in the age group of 51-60 years and 35 (23.3%) cases were there in the 61 years and above category.

Among the controls 72 (48%) subjects were in the age group of 40-50 years followed by 42 (28%) subjects in the category of 51-60 years and 36 (24%) in the category of 61 years and above.

Among the controls 72 (48%) subjects were in the age group of 40-50 years followed by 42 (28%) subjects in the category of 51-60 years and 36 (24%) in the category of 61 years and above.

No significant difference was observed between cases and controls with respect to the distribution according to age group.

Table 2 reveals case group comprised of 111 (74%) males and 39 (26%) females. The control group had 112 (74.2%) males and 38 (25.3%) females. The frequency distribution of study subjects was similar with respect to gender (p-value = 0.895).

Table 3 shows the subjects among the case group were in the pre obese category (64.7%). Only 1.3% and 34% were in obese class 1 and normal category respectively. Among the controls 53.3% were in the normal category and 46.7% were in the pre obese category. A significant difference was seen in the frequency distribution of BMI among the cases and controls. (P value=0.002*)

Table 4 shows the distribution of family history of CHD amongst the study participants. 14 % cases had a family history of coronary heart disease while 87.3% reported no history of coronary heart disease while 8.6% reported no history of coronary heart disease. While control group had family history of CHD in 19% and no history of CHD in 87.3%. No statistical significance was found.

Table 5 shows the distribution of CRP in two categories (≥0.6mg/dl was taken as significant). The CRP level (≥0.6 mg/dl) was significantly higher among the cases (58.7%) compared to controls (41.3%) and in controls <0.6 mg/dl was 41.3% and in controls it was 82.7%. which is statistically significant (p value <0.0001**)

Discussion

Coronary heart disease (CHD) is a multifactorial disease. Various risk factors such as age, gender, family history of heart disease, smoking habit, alcohol intake, Type 2 DM, sedentary habit, obesity, and high blood pressure play a major role in the pathogenesis of CHD. However, despite identification of modifiable risk factors, CHD remains the leading cause of death worldwide. Upto half of all events associated with CHD are reported to occur in apparently healthy individuals who have few or none of the traditional risk factors. As a result, attention has increasingly turned to the roll of other factors, such as inflammation, in the
Atherosclerosis is a complex multifactorial pathophysiology. Recently there has been a wide acceptance of the role of inflammation in the pathogenesis of atherosclerosis and destabilization of coronary artery plaque though the first description of the role of inflammation in coronary artery sclerosis 200 years back. Russell Ross who described first that atherosclerosis is an inflammatory disease.\(^6\) Inflammation in the vessel wall plays an essential part in the initiation, progression, atheromatous plaque formation, destabilization and rupture. Atheromatous material obtained at autopsy have demonstrated the presence of inflammatory mononuclear cells monocytes, macrophages and T lymphocytes in the arterial wall. Endothelial dysfunction and injury triggers a cascade of events that modulates the inflammatory response leading to the recruitments of white blood cell into the vessel wall formation, of foam cell and initiate the development of atherosclerotic lesion.\(^10\)

In view of the importance of role of inflammatory process in the plaque formation and destabilization recent interest has been focused on whether biomarker of inflammation may help to improve risk stratification and identification of patients who may be benefited from particular treatment strategies. Among the inflammatory bio markers (CRP), a prototype marker of inflammatory process has drawn much attention both as a causal factor and in the pre condition of CHD.\(^7\) Multiple prospective cohort studies revealed increased CRP level with wide age range, in both genders with increased CHD risks in primary as well as secondary prevention setting. This findings have been prevalent in different populations with diverse ethnic background and in diverse clinical settings. They also predicted the risk of a variety of cardiovascular outcome such as acute myocardial infarction (AMI), sudden cardiac death and peripheral arterial disease.

<table>
<thead>
<tr>
<th>Family history (CHD)</th>
<th>Case (n %)</th>
<th>Control (n %)</th>
<th>Total (n %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>21 (14.0%)</td>
<td>19 (12.7%)</td>
<td>0.734</td>
</tr>
<tr>
<td>Absent</td>
<td>129 (86%)</td>
<td>131 (87.3%)</td>
<td></td>
</tr>
<tr>
<td>Total (N %)</td>
<td>150 (100%)</td>
<td>150 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

P value=0.734, Chi square value=115

Table 4: Distribution of study subjects according to family history of coronary heart disease (CHD)

<table>
<thead>
<tr>
<th>C-reactive protein</th>
<th>Case</th>
<th>Control</th>
<th>p value (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.6 mg/dL</td>
<td>88 (58.7%)</td>
<td>26 (17.3%)</td>
<td>&lt;0.0001**</td>
</tr>
<tr>
<td>&lt;0.6 mg/dL</td>
<td>62 (41.3%)</td>
<td>124 (82.7%)</td>
<td>(OR=6.769)</td>
</tr>
<tr>
<td>Total</td>
<td>150 (100%)</td>
<td>150 (100%)</td>
<td>(3.972-11.538)</td>
</tr>
</tbody>
</table>

p<0.0001

Table 5: Distribution of study subjects according to c-reactive protein (CRP)

CRP levels have also been shown to predict risk of recurrent ischaemia, acute coronary syndrome, death and percutaneous angioplasty among those with stable and unstable angina. The role of inflammation in unstable angina and MI is evaluated by the histological studies of atheromatous plaque.\(^8\) The release of thromboxane, leukotriene and activated leukocytes in the systemic circulation are found in several studies.\(^9\) No such case control study was available in the literature. Johann A et al., found significant increase in CRP level in the subgroup of patients with AMI (6.49±2 mg/L) in comparison of stable CAD (4.3±2.6 mg/L) (p value 0.02). Other available data also found significantly higher CRP level with unstable angina/AMI compared to stable CAD.\(^14\)\(^16\)

Our results and other corroborative studies revealed an inflammatory bio marker CRP an important pathophysiological implications in patients with acute coronary syndrome. Ischemia induced endothelial damage; oxidized LDL-C, immune complexes and deactivation of dormant cytomegalovirus and viral and plasmid infection are the potential cause of vascular injury is an acute phase response. Whether the elevated CRP is triggering effect of the coronary vascular injury by the aforesaid factors or inflammatory process of the other part of the body that has to be ascertained.\(^17\)\(^20\)

Conclusion
The results of our present study revealed CRP level (≥0.6 mg/dL) significantly higher among the cases 88 (58.7%) compared to control group 26 (17.3%) (p value >0.0001) which is statistically significant. The CRP level ≥0.6 mg/dL was 62 (41.3%) compared to control 124 (82.7%) (p value >0.0001). So we can conclude the individuals who were having CRP level ≥0.6 mg/dL were having higher risk of developing coronary heart disease.

Limitations
The present observation may be taken a new avenue of investigation in the causation of atheromatous plaque formation, progression and destabilization in the causation of unstable angina/myocardial infarction. This is a case control study comprising small number of patient, representing cross section of people of both urban and rural area of Madhya Pradesh and may not represent the whole population of the country. Larger cohort studies are needed to evaluate our observation effectively and adequately.

References

\(\text{Assessed on 27/08/2015.}\)