Evaluation of C-Reactive Protein and Interleukin – 6 as Markers of Coronary Heart Disease

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Background: Coronary heart disease (CHD) is the most common and important cause of morbidity and mortality in western population but incidence has much increased in our population also. This manifests as stable angina (SA), unstable angina (UA) myocardial infarction (MI), chronic IHD – with heart failure and sudden cardiac death. This is due to atheromatous narrowing of coronary vessels which results mainly due to hypercholesterolemia, diabetes mellitus (DM), hypertension and cigarette smoking. Current research has revealed that atherosclerosis is an inflammatory disease and not a simply due to accumulation of lipids in coronary arteries. Recent research in the developed countries is focusing on new biochemical and inflammatory markers.

Objectives: To compare the levels of hs CRP and interleukin-6 in CHD patients and control individuals, with the aim to evaluate their association with CHD patients.

Study Design: This is a case control analytical study. The study was carried out at Armed Forces Institute of Cardiology and Army Medical College Rawalpindi.

Material and Methods: Eighty normotensive and non diabetic individuals comprised of 30 controls (group-A) and 50 CHD patients (group - B) were included in this study. Controls were having normal coronary angiograms. Patients were having abnormal coronary angiograms with single, double or tipple vessel disease. Levels of high sensitivity C-reactive protein (hs CRP) and interleukin-6 (IL-6) were measured by chemiluminescent immunometeric method. Serum glucose, cholesterol, triacylglycerol and urea were measured by enzymatic method. Level of serum creatinine was measured by kinetic colorimetric method.

Results: We compared the values of serum CRP, IL-6, cholesterol and triacylglycerol of group B with control group-A and significance difference was found with p value < 0.05.

Conclusion: Raised levels of hs C-reactive protein and interleukin-6 may have a role in the development of coronary heart disease and can be makers for CHD.

Key Words: Coronary heart disease (CHD), stable angina (SA), unstable angina (UA), myocardial infarction (MI), Diabetes mellitus (DM), high sensitivity C-reactive protein (hs CRP) and interleukin-6 (IL-6).

Introduction

Coronary heart disease (CHD) is a group of closely related syndromes resulting from myocardial ischemia[1]. Hypercholestrolemia, diabetes mellitus, hypertension, smoking, obesity, sedentary life style and diet are already known established risk factors for this disease. Despite the changes in life style, modification of risk factors and the use of new pharmacological approaches to lower plasma cholesterol concentrations, the CHD continues to be the principal cause of mortality and morbidity in the United States, Europe and much of Asia[2].

Alarming increase in smoking, westernized life styles and other CHD risk factors including diabetes mellitus, has been noticed in developing nations. It also has been advocated that soon worldwide incidence of cardiovascular disease (CVD) as a common cause of death will jump from last position (with 26% of all deaths in 1990) to first place (with more than 36% of all deaths in 2020)[3]. According to existing data based on traditional risk factors, India, Pakistan, Bangladesh, Sri Lanka and Nepal have highest incidence rates of CVD as compared globally[4].

CHD results due to atherosclerosis which is a progressive inflammatory disorder of arterial wall, characterized by focal lipid rich deposits in the intimal layer, principally in large medium sized-elastic and muscular arteries which can lead to ishaemia of the heart. Atherosclerosis is clearly an inflammatory disease and does not result simply due to the accumulation of lipids alone where immune mechanisms release the inflammatory cytokines which interact with metabolic risk factors to initiate, propagate and activate lesions in the arterial tree.[5,6]

Inspite of treatment and preventive measures against the established risk factors, adopted strategies have failed to control this killer disease. Currently extensive research is being done for finding new markers to diagnose and identify the individuals at high risk of the disease. Extensive research has emerged with new biochemical and inflammatory markers of CHD, e.g. total plasma homocysteine, microal-

buminuria, cytokines, CRP, serum amyloid-A protein, elevated plasma fibrinogen levels, plasminogen activating inhibitor (PAI) and increased lipoprotein (a) (Ipa) levels. These are increasingly being recognized as an important diagnostic and prognostic markers for CHD.

The fact that several different inflammatory markers with different biological activities contribute to the statistical risk of CHD does not mean that any of the inflamematory markers actually causes the disease but reflects the presence of local inflammatory process in the artery. Further research is required to delineate the role of inflammatory molecules as risk markers as well as contributors to the disease progression[7].

Interleukin-6 (IL-6) is proinflammatory cytokine derived from activated T-lymphocytes that induces the growth and differentiation of B cells to produce antibodies and induction of hepatocyte secretion of acute phase inflamematory proteins. IL-6 signals through a cell surface receptor complex which is almost ubiquitously expressed in most tissues[8]. Epidemiological data evaluating the role of IL-6 in atherogenesis is sparse. In a prospective study in apparently healthy men, elevated levels of IL-6 were associated with increased risk of future myocardial infarction, which supports a role of cytokine mediated inflammation in the early stages of atherogenesis[9]. In fatty streaks and in the atheromatous 'cap' and 'shoulder' regions, macrophage foam cells and smooth muscle cells (SMC) express IL-6, suggesting a role of this cytokine in the progression of artherosclerosis. IL-6 is also associated with elevated levels of C reactive protein and fibrinogen in patients with acute coronary syndrome.[10] Serum levels of IL-6 remained markedly higher in diabetic patients than healthy control subjects which can be the cause of a low level chronic inflammation that may play a key role in the early stages of atherogenesis and in the development of microvascular disorder.[11]

C-reactive protein (CRP) is a nonglycosylated polymeric protein consisting of five identical subunits. CRP was discovered in 1930 and was named for its capacity to precipitate the somatic C polysaccharide of streptococcus pneumonia.[12] It was the first acute phase protein to be described and is highly sensitive systemic marker of inflammation and tissue damage.[13] Measurement of hs CRP has received a great deal of attention recently as to be used as an artherosclerotic risk marker. High CRP response after acute myocardial infarction (AMI) indicate an unfavourable outcome even after correction of other risk factors. CRP constitutes an independent cardiovascular risk factor.[14] In the prospective study of a large cohort of initially healthy middle aged men indicates that modest elevations in serum CRP concentration significantly predict future coronary events. These observations strengthen the association between low grade inflammation and the progression and complications of artherosclerosis.[15]

In stable CHD inflammation is associated with long term adverse effects and hs CRP is an inflammatory marker that predicts further cardiovascular events in healthy subjects and patients with unstable and stable coronary syndrome.[16] In the present perspective this study has been conducted to evaluate these inflammatory markers in our population.

Aim and Objectives

This study has been conducted to compare the levels of C - reactive protein and interleukin – 6 in normal individuals and CHD patients with the aim to evaluate their association with coronary heart disease.

Material and Methods

Setting: The study has been conducted in the Department of Biochemistry and Molecular Biology Army Medical College Rawalpindi. Patients and control individuals were selected from Armed Forces Institute of Cardiology / National Institute of Heart Diseases (AFIC / NIHD) Rawalpindi. Laboratory analysis was done in the Department of Chemical Pathology and CREAM Army Medical College Rawalpindi.

Study Design: This was a case control analytical study conducted on eighty individuals comprised of two groups who were selected by convenient sampling from AFIC.

Group-A (Controls). Thirty individuals having normal ECG, ETT and cardiac enzymes. All these individuals were having normal coronary angiograms.

Group-B (Patients). Comprised of fifty individuals and having CHD on the basis of abnormal coronary angiogram with involvement of single vessel, or double vessel, or triple vessel coronary disease.

Inclusion Criteria: All individuals were normotensive and non diabetic.

Exclusion Criteria: All Individuals with renal diseases, arthritis, pyrexia, hepatitis, malignancy and acute or chronic inflammatory conditions.

Methods: 10 ml venous blood sample was collected after over night fasting of 10-12 hrs. Two ml blood was transferred to test tube containing potassium fluoride for serum glucose assay after centrifugation. Rest of the blood was allowed to coagulate and centrifuged. Serum was stored at -40°C.

Serum glucose[17], triacylglycerol[18] cholesterol[19], and urea[20] were measured by enzymatic colorimetric method. Levels of serum creatinine[21] were measured by kinetic colorimetric method. Levels of interleukin-6 of (IL-6)[22] and high sensitivity C-reactive protein (hs CRP)[23] were measured by chemiluminescent immunometeric method.

Statistical Analysis

All values are given as mean ± standard error mean and statistical comparisons were made by means of student's t –

test. The differences were taken as statistically significant when p value ≤ 0.05. Statistical analyses were performed by using computer programme SPSS 14.0 version.

Table 1: *Comparison of Serum levels of interleukin-6, hs C-reactive protein, total cholesterol and triacylglycerol in Group-A and Group-B. The values are expressed in mean ± SEM. The number of observations is given in parenthesis.*

Study group	Interleukin-6 (pg/ml)	C-reactive protein (mg/L)	Total cholesterol (mg/dl)	Triacylgyrol (mg/dl)
Group – A (30)	3.01 ± 0.18	2.14± 0.13	176.80 ± 4.57	196.70 ± 9.06
Group – B (50)	*6.04 ± 0.67	*7.07± 0.81	*235.56 ± 5.32	*245.32 ± 8.16

*P < 0.05. The values in group B are significantly different as compared to group – A.

Results

Individuals of both groups were non hypertensive and non diabetic confirmed on biochemical evaluation. This evaluation was done by performing various biochemical tests (fasting glucose, urea and Creatinine) in both groups. The levels of inflammatory markers interleukin-6, and hs C-reactive protein were measured in both groups. Age, blood pressure and body weight were also recorded and noted in both groups.

Table 2: *Serum values of fasting glucose, creatinine and urea in group-A and group B. The values are expressed as mean ± SEM. The number of observations is given in parenthesis.*

Study group	Fasting glucose (mg/dl)	Creatinine (mg/dl)	Urea (mg/dl)
Group – A (30)	85.53 ±1.51	0.89 ± 0.02	29.50 ± 1.22
Group – B (50)	88.98 ± 1.29	0.93± 0.02	28.80 ± 1.13

P value > 0.05. The values in group B are not significantly different as compared to Group - A.

Group - A (Control) and Group – B (Patients)

Serum values of interleukin-6 of the individuals in group – A and group-B were 3.01 pg/ml ± 0.18 and 6.04 pg/ml ± 0.67 respectively. Serum values of C-reactive protein of the individuals in group – A and group – B were 2.14 mg/L ± 0.13 and 7.07 mg/L ± 0.81 respectively. Total cholesterol values of the individuals in group – A and group – B were 176.80 mg/dl ± 4.57 and 235.56 mg/dl ± 5.32 respectively. Triacylglycerol values of the individuals in group-A and group-B were 196.70 mg/dl ± 9.06 and 245.32 mg/dl ± 8.16 respectively (Table 1). All these values are significantly different (P < 0.05) between the two groups.

Fasting glucose values of the individuals of group – A and group – B were 85.53 mg /dl ± 1.51 and 88.98 g/dl ± 1.29 respectively. Serum creatinine values of the individuals in group –A and group -B were 0.89 mg/dl ± 0.02 and 0.93 mg/dl ± 0.02 respectively. Serum urea values of the individuals in group – A and group – B were 29.50 mg/dl ± 1.22 and 28.80 mg/dl ± 1.13 respectively (Table 2). There was no significant difference (P value > 0.05) found in the values of glucose, creatinine and urea between the two groups.

Mean age (years) of group-A and group-B was 44.6 and 46.7 respectively. Mean bodyweight (kg) of group-A and group-B was 70.96 and 72.78 respectively. Mean values of systolic and diastolic blood pressure of group-A and group-B were 120/79 mm Hg and 121/79 mmHg respectively. The above mention values of group-A were compared with the respective values of group – B.

No significant difference was found in the mean values of age, body weight and blood pressure of group –A and group-B.

Discussion

The pandemic of CVD emerged in the beginning of the 20th century as a 4th most common cause of death in Industrialized countries, which achieved first place by the end of first decade. Although much has been learnt about the causes of CHD but the gaps in the knowledge are noteworthy and fully half of all the patients with this disease do not have any of the established risk factors. Death due to CHD has much increased in developing nations also. Cholesterol screening fails to identify almost 50% of those individuals who will present with acute coronary syndrome (ACS).[24,25] New knowledge about inflammation in CHD has provided surprising insights into its pathogenesis and serum markers of inflammation provide an evenue of its complications. Circulating inflammatory markers such as CRP, fibrinogen and interleukins (especially IL-6) are increased in high-risk group patients and predict future risk. It is still unclear whether the different inflammatory markers merely are markers or they actively contribute to the development and progression of atherosclerotic disease at their own. Further research in required to delineate the role of inflamematory markers which will provide new opportunities for diagnosis and prediction of disease and will lead to new treatments for this life threatening disease.[26-28]

Inadequate number of studies relating to inflammatory markers are available in literature particularly in population which is non hypertensive and non diabetic. No study has been conducted on the above-mentioned population in Pakistan. In our study population inflammatory markers of group-A (control) and group B (patients) are presented here for discussion and comparison with other available data.

In group-A values of interleukin-6 and C-reactive protein were 3.01 pg/ml ± 0.18 and 2.14 mg/L ± 0.13 respectively. In group-B values of interleukin-6 and C-reactive protein were 6.04 pg/ml ± 0.67 and 7.07 mg/L ± 0.81 respectively.

When we compared values of these parameters of group-A with the group-B for p value calculation a significance difference with p value < 0.05 was found in the values of above mentioned parameters of group-A and group-B which is similar with available data.

In a study conducted by Biasucci and his colleagues on inflammatory markers reported that levels of IL-6 > 3 pg/ml were found in 61% patients of unstable angina as compared to stable angina, in which only 21% patients were having IL6- levels > 3 pg/ml[29]. Like wise in an other study patients with restenosis, however showed significant increases in IL-6 concentrations, at one hour (p<0.03) and six hours (P< 0.01) post procedure, with 3.6 and 4.4 fold increase in IL-6 respectively. Circulating IL-6 concentrations at six hours after the procedure in the group with restenosis also exceeded the normal range[30]. In another study conducted on the CHD patients have shown the association of IL-6 as risk assessment inflammatory marker. In the same study levels of TNF, IL-6 were found raised in patients with ACS[31]. Assessment of IL-6 has shown that elevated IL-6 levels are strongly associated with future cardiac events and mortality in a population with stable CHD during a long term follow up. Each increase of 1 pg/ml in IL-6 was associated with increased chances of subsequent MI or sudden death[32]. In our study the levels of IL-6 have been found significantly raised with p value < 0.05 and support the idea that IL-6 can be used as prognostic marker in clinical setup. During long term follow up the proinflamamtory activity of IL-6 remains elevated in ACS patients supporting the concept of systemic rather than a local vascular inflammation contributing to the development of artherosclerosis[33]. Elevated concentrations of CRP and IL-6, but not IL-18 were independently associated with risk of CHD in subjects from the area with moderate absolute risk. A comparison of elevated levels of inflammatory markers i.e. CRP, IL-6, serum amyloid - A protein and total homocysteine with traditional CHD risk factors indicated that IL-6 and homocysteinuria were the strongest independent biomarkers for CHD related death.[34,35] Values of IL-6 in patient group in our study were raised and significant when compared with values of IL-6 in control group. Raised level of IL-6 in the available data supports the findings in our population. This reveals that simultaneous assessment of markers of inflammation and lipid metabolism may improve cardiovascular risk in patients with stable CHD.[36]

Inspite of limitations of CRP as an inflammatory marker for screening the persons at risk for CHD, the available data suggests that hs CRP has the potential, to play a role for risk assessment and recommending preventive measures for prevention of CVD. Elevation of CRP level is a common finding in unstable angina and probably indicates the presence of evolving inflammation at coronary atheroma. In such patients CRP level of 10.5 mg/L provided optimum sensitivity and specificity for adverse outcome[37]. In another study of patients with severe CHD hs CRP has strong predictive value of AMI in patients of unstable angina. In these patients hs CRP values were highly significant as compared to those patient of unstable angina or stable angina who did not develop AMI.[38,39] The results of our study are conistent with the findings of studies discussed so far.

In a follow up study of patients who were admitted in hospital with angina pectoris hs CRP levels were measured at the time of a admission. After discharge, during the period of 13 month follow up the patients who were having CRP levels 30.61 mg/L developed unstable angina and AMI as compared to those with CRP levels 10.48 mg/L at the time of admission. Speed Well study on incidence CHD suggested that the measurement of CRP may be logical and practical to assess the enhancement of current risk stratification.[40,41]

In a cross sectional study more visceral fat in south Asians had a strong (p< 0.01) correlation with CRP when compared with Europeans. This suggests that visceral adipose tissue may be an important contributor to low grade chronic inflammation leading to increased risk of CHD in this ethnic group. Similarly levels of hs CRP were significantly higher in healthy male Indian Asians than European whites, which may contribute to the increased CHD risk among Indian Asians.[42,43]

Similarly in a study carried out in United States, the young healthy Asian Indians were found to have both greater insulin resistance and higher hs CRP levels when compared with Caucasians, which shows that an underlying pro inflammatory state may contribute to their increased risk for both type –II DM and CVD [44]. In another study the altered CRP concentrations were not related to the increased prevalence of CHD in non-diabetic UK resident Indo Asians[45]. CRP levels have also been shown to predict risk of both recurrent ischaemia and death among the patients of stable and unstable angina, who were treated by angioplasty and those presenting to emergency rooms with ACS[46].

Further more in patients with ACS the CRP levels were significantly raised at the time of admission as compared to controls. Moreover during follow up CRP was higher in those patients who underwent angioplasty as compared to those on conservative management[47].

In a large prospective study evaluation of hs CRP and its comparison with other inflammatory markers in the prediction of CHD, it has been reported that CRP is a relatively moderate predictor of CHD and suggests that more studies are required for evaluation of CRP as risk marker for CHD[48].

If we recall the discussion made about CRP in the previous paragraphs holistic picture emerges which convincingly advocate that the CRP levels are raised in all forms of CHD, which is consistent with the findings of our study. When we compared the values of total cholesterol and

triacylglycerol of group-A with group-B there was significant difference with P< 0.05 (Table 1). This result is consistent with a study in which lipid level were found raised in conjunction with increased level of IL-6 level[36].

From the above mentioned discussion it is evident that inflammatory markers not only identify the individuals at risk but they may be contributory factor to the development and progression of the disease which is consistent with this study. In our study no inference could be drawn regarding disease epidemiology in females because only few female patients fulfilling the inclusion criteria could be inducted in the study.

Conclusion

Raised levels of interleukin-6 and hs C-reactive protein may have a role in the development of coronary heart disease. More larger group studies are required to establish the link of these markers with the disease.

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