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Original Article

C-Reactive Protein in Angiographically Documented Stable Coronary Disease

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Background: The association between C-reactive proteins (CRP), a marker of inflammation, and major coronary risk factors has been highlighted in several investigations. CRP is associated with acute cardiac events and can predict their occurrence. The aim of this study was to evaluate the association between CRP serum level and coronary artery disease (CAD) along with it's major risk factors, in patients with stable angina pectoris.
Patients and Methods: In a cross-sectional case control study, CRP and major coronary risk factors including cholesterol, diabetes mellitus (DM) smoking and hypertension were evaluated in 200 angiographically documented CAD (case group) and 120 subjects with normal coronary arteries(control group).
Results: Of 320 subjects 50 in both case and control groups were presented with a CRP≥6 mg/dl, with 30 (60%) female and 20 (40%) male patients. There was a significant association between CRP≥6 mg/dl and those with age>60 years (P=0.002), hypertensive subjects (P<0.05), diabetic patients (P<0.05), hypercholesterolemic patients (P<0.05), Low HDL (P<0.05) and smokers (P<0.05) in both the case and control groups. Multivariate analysis showed a significant correlation with CRP and angiographically documented CAD independent of coronary risk factors.
Conclusion: The present study showed a significant relationship between C-reactive protein levels and coronary risk factors and also demonstrated an independent relationship between angiographically documented CAD and elevated CRP serum levels in patients with chronic stable ischemic heart disease

Key words: C-Reactive Proteins, Coronary Artery Disease, Angiography

Introduction

Coronary artery disease remains the leading cause of death worldwide.[1] The vascular endothelium is subject to injury from numerous potential insults including coronary risk factors (high cholesterol, smoking, hypertension, and diabetic mellitus), oxidative stresses and hemodynamic forces, resulting in endothelial dysfunction. Coronary endothelial dysfunction leads to compensatory response, thereby increasing the adhesiveness as well as the permeability. Coronary atherosclerosis is the end point of this pathology.[2] It is supposed that local and systemic inflammation plays a role in the initiation and progression of atherosclerosis and its complications.[2,3]

Acute phase proteins including C-reactive proteins (CRP) are numerous proteins synthesized by the liver in response to products of damaged cells during infections, malignancy, and inflammatory or neoplastic disease and are valuable markers of disease activity (and response to therapy). The precise biological

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function of CRP is not fully understood, but its properties are consistent with an important role in nonspecific defense mechanism. It has long been known that CRP levels are elevated in the presence of risk factors of CAD, including smoking, diabetes, obesity and elevated blood pressure.[4,5] Many studies indicate that the relation between CRP level and future cardiovascular risk is independent of coronary risk factors. Elevated plasma CRP is also associated with obesity, insulin resistance and hyperglycemia, suggesting that insulin resistance, type 2 diabetes and CAD may be consequences of the ongoing acute phase response, reflecting a chronic adaptation of the immune system.[4,5] Emerging data, however, suggest that CRP may be a mediator as well as a marker of atherosclerosis. CRP induces expression of cellular aphelion molecules, interlukin-6, and endothelin-1 by endothelial cells. CRP also mediates monocyte chemoattractant protein-1 induction, which in turn mediates the uptake of LDL by macrophages. Furthermore, smooth muscle cells and macrophages in the arterial tissue have been shown to produce CRP that is substantially unregulated in atherosclerotic plaque.[6] After premature myocardial infarction (MI), CRP level appears to be a more powerful predictor of cardiac and total death than ejection fraction, which was previously shown to be the most significant indicator of prognosis.[5] CRP is elevated in acute MI, probably as a response to myocardial injury.[1]

Patients and Methods

200 angiographically documented CAD patients (101 males and 99 female, aged 58 ± 10) and 120 angiographically documented normal coronary artery control subjects (68 males and 52 females, aged 55 ±7) entered in this cross-sectional, case-control study. The indication for coronary angiography was suspicion to CAD in both the case and the control groups. The individuals with a history of myocardial infarction or unstable angina during the previous 4 weeks, as well as subjects with a history of percutaneous transluminal coronary angioplasty (PTCA), were excluded from the study. Furthermore, individuals with concomitant systemic disease (rheumatic disease, chronic liver disease, renal disorders, cancer, and recent infectious disease), as well as patients with surgical procedures in the preceding 3 months, were excluded from the study. Coronary angiographies were performed in catheterization lab of Namazi hospital in Shiraz-Iran according to the standard Judkins technique. All angiograms were reviewed and estimation of percentage of coronary stenosis was done by a cardiologist without taking an account of CRP level. For better evaluation, all the coronary lesions less than 50 percent stenosis were omitted from the study. The patients were classified as CAD if one or more coronary arteries had a stenosis ≥50%. Patients with completely normal coronary arteries were selected as the control group. Major risk factor assessment (hypertension, diabetic mellitus, smoking and hypercholesterolemia) was done in both study and control groups. Blood samples were obtained after 12 hrs fast on the day before angiography for evaluation of FBS, total cholesterol, HDL and LDL cholesterol as well as ultra sensitive CRP.

Hypertension was defined as the sitting systolic blood pressure>=140 mmHg and/or diastolic

blood pressure >=90 mmHg. Current smoking was defined as those who had smoked in the month before the blood sampling. Diabetes was defined as fasting blood glucose >= 126 mg/dl or a diagnosis of diabetes needing drug therapy. Hypercholesterolemia was defined as total cholesterol >=200mg/dl or LDL cholesterol >=130mg/dl or a history of hypercholesterolemia.

CRP levels were determined in case and control groups by AVITEX-CRP-LATX TEST, which is a rapid latex agglutination kit for the detection of C-Reactive in human serum with a detection limit of 6mg/litre of CRP in the patient's serum. Positive results were obtained at a CRP serum concentration above 6mg/liter and negative results were obtained at 6mg/litre and below.

All data were presented as mean standard deviation except for CRP levels, where median, 20^{th} and 80^{th} percentiles were given. Baseline demographic and biochemistry analytical information was presented as a range for continuous variables and as absolute percentage for categorical variables.Associations between two categorical variables were tested accurately by Chi-Square test, or Fisher's exact test. Stepwise multiple regression analysis was performed to evaluate the relationship of our explanatory independent variables to the response variable under study. Statistical analyses were performed with SPSS software for windows version 10. Two- tailed P-values <0.05 were considered as statistically significant.

Results

Table 1 shows the baseline characteristic of the study participants. 101 men and 99 women (case group), and 68 men and 52 women (control group) were entered in this study.

Mean age in the case group was 58.1±10.2 while in the control group it was (55.2±10.3). 74 subjects (37%) in the case group and 25 (20.8%) in the control group were older than 60 years (P=0.002). In the case group, the mean of HDLC was 40.1± 5.2, of TC was 230.4±10.3, of LDLC was 140.6±30.4 and of TC was 235.2±10.7; whereas in the control group, the mean HDLC was 45.1±10.3 , TC was 200.6±10.1, LDLC was 130.4±10.4 and TG was 200.8±10.2. 70 (35%) patients in the

Table 1. The baseline characteristics of population under study.

	Case	Control	P values
Sex F/M	101/99	68/52	.285
Age 60 Y	74 (37%)	25 (20.8%)	.002
Hypertension	70 (35%)	30 (25%)	.042
Diabetes	55 (27.5%)	18 (15.0%)	.010
Smoking	87 (43.5 %)	46 (38.3%)	.360
Triglyceride>=150 mg/dl	109 (54.5%)	71 (59.2%)	.410
Total cholestero>=200 mg/dl	84 (42.0%)	36 (30.0%)	.030
HDL<35 mg/dl	70 (35.0%)	20 (16.7%)	<0.05
CRP>= 6 mg/l	41(20.5 %)	9 (7.5 %)	.002

Table 2. Association between 50 subjects with positive CRP and coronary risk factors.

		CRP>6 mg/l	P value
SEX	Female Male	30 (60%) 20 (40%)	0.258
AGE year	60 <60	34 (68%) 16 (32%)	<0.05
HTN	yes no	40 (80%) 10 (20%)	<0.05
DM	yes no	37 (74%) 13 (26%)	<0.05
SMOKING	yes no	32 (64%) 18 (36%)	<0.05
TG Mg/dl	150 <150	34 (68%) 16 (32%)	0.065
CHOL Mg/dl	200 <200	35 (70%) 15 (30%)	<0.05
HDL_C Mg/dl	35 <35	12 (24%) 38 (76%)	<0.05

case group had hypertension, compared to 39 (25%) in the control group (P=0.042). Similarly, the diabetic patients in the case group were more prominent (27.5% in the case group versus 15% in the control group) (P=0.01). 35% patients in the case group and 16.7% in the control group had HDL<35mg/dl (P<0.05). Neither a statistically significant difference was observed for smoking in the case (43.5%) and in the control (38.3%) groups (P=0.360) nor a difference in TG 150≥mg/dl in the case group (42%) and the control group (59.2%) (P=0.410).

Table 2 shows the association between risk factors and CRP≥6 mg/dl in both the case and the control groups.

In 50 subjects with CRP≥6 mg/dl, 30(60%) of them were female while 20(40%) were male (P=0.210).

There was a significant association between those with CRP≥6 mg/dl and age >60 years (P<0.05), between CRP≥6 mg/dl and presence of hypertension in both the groups (P<0.05), as well as between CRP≥6 mg/dl and presence of diabetes in both groups (P<0.05). On the other hand, smokers also showed a significant correlation with positive CRP (P<0.05). A positive correlation with positive CRP was present among those with cholestrol≥200 mg/dl (P<0.05) but not among those with TG≥150 mg/dl (0.065).

We adjusted these coronary risk factors with multivariate analysis and finally found that angiographically documented CAD had significant correlation with positive CRP (P<0.05).

Discussion

Acute phase proteins including C-reactive proteins (CRP) is an acute phase protein synthesized by the liver and stimulated by innumerable products of damaged cells during the inflammatory process, and are tremendous valuable markers of disease activity and response to therapy, in tissue damaging, inflammatory , infective or neoplastic conditions.[6,7] Median CRP values are typically 1-2 mg/l in healthy persons, which eventually double with age from 30-60 years and tend to be higher in females than males.

Rifai et al.[9] found no association between of inflammatory markers in men with angiographically documented coronary heart disease, but Tatru MC,[10] in 2000, in a large trial study, showed relation between severity of atherosclerosis in patients with myocardial infarction, and CRP. Rettersal L[5] in 2002 showed that elevated CRP predicts death in patients

with previous premature myocardial infarction. Yasojmak[11] in 2001 showed that activated complement may attack cells within the atherosclerosis plaque , thereby establishing a self-sustained autotoxic mechanism leading to plaque instability and cardiac events, thus the high levels of CRP may indicate plaque instability and cardiac events. Grisselli M[12] showed that high levels of CRP before the acute MI worsen the outcome. Lee WH[13] in 1997 showed that CRP may promote blood clotting possibly mediated through tissue factor or other thrombogenic proteins.

The present study showed the relationship between C-reactive protein levels and coronary risk factors (diabetes mellitus, hypertension, hypercholesterolemia and smoking). Also, our study demonstrated an independent relationship between angiographically documented CAD and elevated CRP serum levels in patients with chronic stable ischemic heart disease. This association indicates the role of inflammatory process in the pathogenesis of atherosclerosis in coronary arteries.

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