ejpmr, 2016,3(7), 326-329.

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

STUDY OF LEVELS OF C-REACTIVE PROTEIN IN CORONARY ARTERY DISEASE AND DIABETES MELLITUS

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Article Received on 28/04/2016 **Article Revised on 18/05/2016** **Article Accepted on 08/06/2016**

ABSTRACT

Coronary Artery Disease (CAD) leads to Angina and Myocardial Infarction (MI). Premature mortality on Coronary Heart Disease (CHD) is more common in diabetic atherosclerosis. In the present study serum level was C-Reactive Protein estimated in patients of CAD with DM, CAD without DM, DM without CAD and CAD with DM and other risk factors compared to healthy normal subjects. The level of C-Reactive Protein was significantly increased in all four groups of patients as compared to control group. **Conclusion–** The independent prognostic utility of quantifying systemic inflammation suggests that CRP and other inflammatory molecules as disease process markers of atherosclerosis may be excellent tools in CAD prediction.

KEYWORDS: Coronary Artery Disease, Diabetes Mellitus, C-Reactive Protein.

INTRODUCTION

C – reactive protein (CRP) was first detected in 1930 by Tillet and Frances, who identified a substance in the sera of patients acutely infected with pneumococcal pneumonia that formed a precipitate when combined with polysaccharide C of Streptococcus Pneumoniae.[1] It was found subsequently that this reaction was not unique to pneumococcal pneumonia but could be observed with a large variety of other acute infections and inflammatory states.

CRP is a calcium- binding pentameric protein consisting of five identical, noncovalently linked, 23-KDa subunits.[2] It is present in trace amounts in humans and appears to have been highly conserved over hundreds of millions of years.[3] CRP is synthesized primarily by hepatocytes in response to activation of several cytokines, such as interleukins 1 and 6, and tumor necrosis factor-α (TNF- α). Because the clearance rate of CRP remains constant, its serum level is determined only by its rate of production.

C – reactive protein is synthesized by the liver and its functions are uncertain, it seems to play a role in tissue inflammation and binds to complement Clq.[4] It is a known acute phase marker of tissue injury, infection and inflammation.

Despite overwhelming evidence that CRP is an independent predictor of coronary events, several issues remain unresolved so far. First, it is not known whether increased CRP production reflects arterial inflammation or inflammation elsewhere in the body.[5] This can have important implications for therapy, for example systemic therapy for risk reduction (aimed at lowering CRP levels and / or reducing inflammation) versus local therapy (eg. angioplasty and bypass). The first approach may more effectively prevent acute coronary events than the second more invasive one.[6]

Second equally important but yet unresolved issue is that whether CRP has a pathogenic role in CAD or its levels rise merely as a result of inflammation. CRP is known to selectively bind to LDL, particularly the partly degraded LDL found within atherosclerotic plaques and is

generally present with it and activated complement, within such plaques.[7] Bound CRP activates complement, is pro- inflammatory and may thus contribute to atherogenesis. The third related issue is that of effect of lowering CRP levels on atherosclerosis process. Statins are Known to lower CRP levels, suggesting that some of their beneficial effects may be mediated via suppression of inflammation. Recently, trimtazidine was shown to significantly lower plasma CRP levels in patients with acute MI.[8] Despite these isolated findings, it will be possible to definitely know whether CRP has a pathogenetic role only when drugs are developed that selectively inhibit CRP production or binding. The efficacy of correcting CRP levels has also not yet been tested, it will need to be done, including in special populations such as the elderly.[9]

The fifth issue is a purely practical one, that of measurement of CRP. Should it be done in all patients of CAD; only in symptomatic patients, or may be in all adult males and post-menopausal females. For this, sensitive and cheap assays need to be developed first.

It is likely that a sensitive CRP assay may in fact become a new risk assessment marker for cardiovascular disease and guidelines for its application are under discussion.

Currently, it is certain that in those patients who have CAD, raised CRP levels do indicate a high risk group, which may require intensive management.

The rupture of vulnerable plaque is the most important mechanism by which atherosclerosis leads to the acute ischaemic syndromes of unstable angina, acute myocardial infarction and sudden cardiac death.[10] These vulnerable plaques are lipid rich atheromatous plaques that have a thin fibrous capsule.[11] However the specific mechanisms responsible for plaque weakening have not been clearly determined. There is substantial evidence implicating an inflammatory process in the pathogenesis of acute coronary syndromes. Local inflammatory cells can generate and release cytokines that have potential to activate the endothelium transforming its natural antiadhesive and anticoagulant properties. Furthermore, inflammatory cytokines may reduce matrix synthesis and increase its degradation, favouring plaque rupture. Finally cytokines may enhance endothelin synthesis in endothelial cells and macrophages resulting in increased smooth muscle reactivity to local vasoconstrictors. The evidence supporting this hypothesis that inflammation is critical in the pathogenesis of acute coronary syndromes comes from a variety of sources.

Although the evidence is strong in support of CRP as an independent risk factor for ischemic heart disease, the mechanisms underlying the association are unclear. However, recent data suggest a direct pathogenic role for CRP in atherosclerosis.[12] The rates of coronary events increase significantly with increased in the baseline levels of CRP. In a randomized trial lovastatin therapy reduced CRP level significantly by 14.8%, an effect not explained by lovastatin induced changes in lipid profile.[13] Statin therapy thus may be effective in the primary prevention of coronary events among persons with relatively low lipid levels but with elevated levels of CRP.[14]

MATERIALS AND METHODS

The present study was carried out in the Department of Biochemistry, Dr. D.Y. Patil Education Society's Medical College and Hospital, Kolhapur. This study was approved by Institutional ethical committee.

In this study a total number of 200 subjects between age 40 yrs to 60 yrs matched with age and sex were included. They were distributed in controls and four groups.

Controls	Normal Healthy controls- 100 cases
Group- I	Patients with CAD and DM- 25 cases
Group- II	Patients with CAD – 25 cases
Group- III	Patients with DM – 25 cases
Group- IV	Patients with CAD and DM + Other risk factors- 25 cases

All controls were from the same age groups as patients, not showing any clinical signs and symptoms suggestive of CAD. They were having normal blood pressure (BP), ECG, blood sugar level and apparently no other cardiac risk factors. Group-I contained patients diagnosed to have CAD(based on angiography) with confirmed DM and were receiving treatment for the same Group- II contained patients with CAD but no DM Group-III contained Type II DM patients receiving treatment for DM and were not showing any complications of DM, and had normal ECG and BP. Group- IV contained patients with CAD and DM along with other risk factors. (such as smoking, hypertension, family history of CAD, obesity etc.).

Sample collection

4 ml of venous blood was collected in plain bulb and was allowed to clot. Serum was separated by taking necessary precautions to avoid haemolysis. This serum was used for the estimation C-Reactive protein.

Inclusion Criteria

A) Control group: 100 age matched healthy subjects were included in the control group. The subjects were

selected after screening for any prior history of cardiovascular disease or any other disease. B) CAD Patients: Angiographically proven patients by the cardiologists with relevant coronary artery disease showing greater than 50% stenoses in at least one major coronary artery at the time of diagnostic catheterization were enrolled in this study. Each subject was screened by a complete history, physical examination and laboratory analysis. C) Diabetic Patients with CAD: Clinically diagnosed patients whose fasting blood glucose level was above 125 mg/dl.

Exclusion Criteria

The patients with hemodynamically significant valvular heart disease undergoing catheterization, surgery or trauma, known cardiomyopathy, known cancer, abnormal hepatic and renal function, past or concurrent history of any disease and taking any medication that could influence the oxidant and antioxident status and endothelial functions were exduded from the study group.

RESULT

Showing the levels of CRP in (mg/dl) in control subjects and different study groups

Groups	CRP (mg/dl)
Control	3.8 ± 1.82
Group I (CAD with DM)	16.7 ± 14.67 *
Group II (CAD with out DM)	12.1 ± 18.1 #
Group III (DM with out CAD)	15.5 ± 13.51 *
Group IV (CAD with DM and other risk factors)	20.4 ±11.03 * ♣ ♠

Values are expressed as mean ± SD
* P<0.001 Group I, III, IV as compared to control
# P<0.05 Group II as compared to control
♣ P<0.001 Group IV as compared to Group II
♠ P<0.05 Group IV as compared to Group III

In the present study sr. CRP was found to be significantly increased in all four groups of patients as compared to control Group.

Similarly significant rise in serum CRP was observed when Gr. IV was compared with Gr. II and Gr. III.

DISCUSSION

The acute-phase response is a major pathophysiologic phenomenon that accompanies acute or chronic inflammation. Acute-phase proteins are defined as proteins whose plasma concentrations increase or decrease by at least 25% during inflammatory states. Measurement of serum levels of acute-phase proteins is useful, because it may reflect the presence and intensity of an inflammatory process. The most extensively studied indicator of the acute-phase response in cardiovascular disease (CVD) is CRP.

In the present study sr. CRP was found to be significantly increased in all four groups of patients as compared to control group.

Similarly significant rise in serum CRP was observed when Gr. IV was compared with Gr. II and Gr. III.

Postulated mechanisms for the association between CRP and the development of CHD include a possible relationship to the extent of coronary atherosclerosis or the extent of inflammation within the atherosclerosis present.

Several lines of evidence suggest a role for CRP in predicting the presence or absence of atherosclerosis. Firstly, CRP is related to standard cardiac risk factors and has been identified within atheroma, particularly co-localized with foam cells. Secondly, inflammation is an essential component in the development of atherosclerosis.

The strong association of inflammatory markers with atherothrombotic coronary events in humans provides clinical evidence, supporting basic data on the role of inflammation in promoting coronary plaque instability[15-17] and thrombotic potential. In previous reports, CRP has been more consistently identified within atheromatous and potentially vulnerable plaques compared with fibrous plaques.[18]

The presence of inflammation has been noted since the earliest histologic observations and theories on the development of atherosclerosis. An acute-phase reactant, hs- CRP plays an important role in the innate immune response and is now recognized as a mediator of atherothrombotic disease. Recent evidence has shown that CRP directly participates in the atherothrombotic process by activating complement, regulating endothelial nitric oxide (NO) synthase expression and NO synthesis, upregulating expression of cellular adhesion molecules, and possibly directly modulating oxidation of LDL.[19]

CRP is known to selectively bind to LDL, particularly the partly degraded LDL found within atherosclerotic plaques and is generally present with it and activated complement, within such plaques.[7] Bound CRP activates complement, is pro-inflammatory and may thus contribute to atherogenesis.

Observations in the present study ie. Increased level of CRP and LDL supports the possibilities discussed above. CRP bound to LDL activations complement and thus contributes to the atherogenesis which is an inflammatory process.

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