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Research Article

ROLE OF MCP-1 IN FIRST TIME VS RECURRENT MYOCARDIAL INFARCTION

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A B S T R A C T

Objectives: This study was undertaken to explore the role of MCP-1 in acute myocardial infarction (MI).
Background: MI is followed by an inherent and extensive inflammatory reaction leading to a plethora of cytokines released by the injured myocardium regulating tissue repair and the subsequent host outcome. Monocyte Chemoattractant Protein (MCP)-1 , a CC chemokine is greatly expressed in atherosclerotic plaques and has an established fundamental role in initiation and progression of atherosclerosis.
Methods: This study was conducted in the Department of Biochemistry, Lady Hardinge Medical College & associated SSKH in collaboration with the Department of Cardiology, G B Pant Hospital, New Delhi. Patients of Myocardial Infarction (MI) presenting within 24 hours of the event were recruited in 2 groups group A consisted of 100 patients of MI who do not have a family history of MI and group B consisted of 100 patients of MI who had a family history of MI. Each of these groups was further divided into 2 subgroups - patients with first time MI and patients with recurrent MI .Blood samples were evaluated for serum MCP-1 by ELISA.
Results: Patients with recurrent MI had higher serum levels of MCP-1 compared to patients with first time MI (p= 0.064) .Serum MCP-1 was significantly raised (p=0.049) in MI with a positive family history of MI.
Conclusions: MCP-1 has a key role in atherosclerosis and may be an encouraging biomarker for risk prediction in patients with coronary artery disease.

INTRODUCTION

Elaborate inflammatory reaction and cytokine expression are intrinsic components of host response after myocardial infarction (MI) .Thearray of cytokines released by the injured myocardium regulate tissue repair and the subsequent host outcome.Chemokines are a subset of inflammatory cytokines that play a role in the recruitment of leukocytes to sites of inflammation and are grouped into subfamilies: CXC chemokines and CC chemokines. Monocyte Chemoattractant Protein (MCP)-1 or CCL2 is a CC chemokine which is greatly expressed in atherosclerotic plaques (1). Acting through its receptor CCR2, it mediates monocyte infiltration in the atheromatous lesion and the accumulation of lipid-laden foam cells (2,3).

Monocytes play a fundamental rolein initiation of the fatty streak, promotion of plaque instability, as well as remodelling and restenosis after MI (4, 5). Besides this, MCP-1 has been implicated to have myriad of roles in the development of atherosclerosis like regulation of tissue factor expression, interference in nitric oxide synthesis, promotion of proliferation and migration of the smooth muscle cells, participation in oxidative stress and neovascularization of the atheromatous plaque making it unstable (4-7). MCP-1 thus has an established crucial role in initiation and progression of atherosclerosis.

Since atherosclerosis is a chronic inflammatory state, the biochemical markers of inflammation form a bedrock of potential non-invasive indicators of risk assessment and prognosis of recurrent cardiovascular events following an acute coronary syndrome (ACS) (8), and are the subject of intense investigation. Since patients of coronary artery disease (CAD) are at a greater risk of recurrent cardiovascular events and premature deaths, risk prediction and secondary prevention of CAD patients should be the primary focus. This study was undertaken to evaluate the role of MCP-1 as an

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inflammatory biomarker in acute MI in first time or in recurrent event.

METHODS

The prospective observational study was conducted in the Department of Biochemistry, Lady Hardinge Medical College & associated SSKH in collaboration with the Department of Cardiology, G B Pant Hospital New Delhi. Ethical clearance was obtained from Institutional Ethical Committees.

Patients of Myocardial Infarction presenting within 24 hours of the event to Cardiology department / Emergency of GB Pant hospital were enrolled after confirmation of the diagnosis by clinical Evaluation, ECG and blood tests as per accepted criteria. The patients were enrolled in the study after informed consent. Patients of diabetes mellitus, cancers, patients of chronic liver disease, chronic kidney disease, diseases of inflammatory pathology like arthritis were excluded from the study. Patients were divided into two main groups which were further divided into two subgroups each:

Group A: Patients of MI who do not have a family history of MI- 100 patients
Group A1: Patients who had MI for the first time (n= 53 enrolled)
Group A2: Patients who had recurrent MI (n= 47enrolled)
Group B: Patients of MI who have a family history of MI-100 patients
Group B1: Patients who had MI for the first time (n= 54 enrolled)
Group B2: Patients who had recurrent MI (n= 46 enrolled)
Five milliliter (5 ml) of peripheral blood was collected using all aseptic procedures, from all the participants within 24 hours of MI after confirmation of the diagnosis by clinical evaluation, ECG. Informed consent was taken before sampling. Blood sample was collected in vacutainer with clot activator and was used for the obtaining serum after centrifugation at 2000 rpm for 10 minutes. Serum was stored at minus 20 degrees before it was batch analyzed for MCP-1 by ELISA.

Serum levels of MCP-1 were measured using Human MCP1 ELISA kit by Diaclone SAS, France (Batch: MCP1-08, Catalog No.873.030.096). The absorbance of the coloured complex was measured at 450nm wavelength within 15 minutes after adding the stop solution using TECAN Infinite f200 Pro ELISA plate reader and the generated OD values for each standard were plotted against expected concentration forming a standard curve.

Statistical Analysis

The data obtained was entered into Microsoft Excel Worksheet. Statistical analysis was performed using statistical software package statistical package for the social sciences (SPSS) version 22.0 (IBM Corporation, Armonk, New York, United States). Data are represented as mean ± standard deviation; mean value of the continuous variable was compared using t-test. The Pearson's correlation coefficient was calculated to assess the correlation between two continuous variables. Value of $p< 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

It is a well established fact that atheromatous lesions are abundant with macrophages. Several factors such as hemodynamic forces (9), oxidative stress (10), and modified lipoproteins (11) cause injury to vascular endothelium , and the injured epithelium express adhesion molecules such as vascular adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), endothelins and selectins that bind to leukocytes (12) . There is accumulation of LDL in the endothelium, which after forming oxidised LDL is engulfed by monocyte-derived macrophages. These lipid-laden foam cells constitute a key element of the fatty streak (13, 14). Cytokine and chemokine production is induced by these foam cells and this leads to the recruitment of additional circulating immune cells. Thus, Inflammation plays a cardinal role in the pathogenesis of atheromatous lesion, widespread inflammation being associated with acute and unstable coronary events (15, 16).

MCP-1 is the most extensively characterized CC chemokine and a potent chemotactic factor for monocytes. It is produced by a variety of cell types like endothelial, fibroblasts, epithelial, smooth muscle, mesangial, astrocytic, monocytic, and microglial cells, either constitutively or after induction by oxidative stress, cytokines, or growth factors (17, 18) .

However, the major source of MCP -1 is the monocyte/macrophages (19). MCP-1modulates the migration and infiltration of monocytes, memory T lymphocytes, and natural killer (NK) cells. There is enough evidence that supports that MCP-1 plays a dominant role in the recruitment of macrophages in atheromatous lesions. In LDL receptor deficient mice (20) and in animals over expressing human apolipoprotein B (21), deletion of the MCP-1 gene majorly reduced macrophage recruitment in the aortic wall. In apoE null mice fed with a high-fat (22) or a regular chow diet (23), deletion of CCR2, the receptor for MCP-1, attenuated macrophage accumulation in atherosclerotic lesions. Formation of new atherosclerotic plaques in hypercholesterolemic mice was impaired by MCP-1 inhibition using transfection with an N-terminal deletion mutant of the MCP-1 gene (24).

In the present study , patients of MI who had a positive family history of CAD had significantly raised serum MCP-1 levels as compared to patients who had MI but had no family history ($p=0.049$) indicating a strong genetic predisposition(Fig 1) .

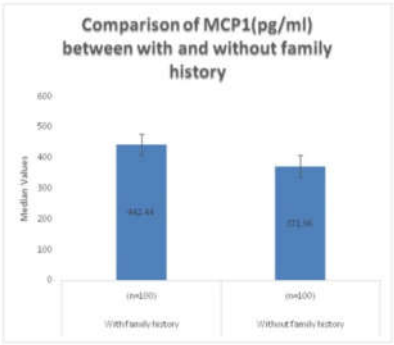

Fig 1 Patients with a positive family history of CAD significantly raised serum MCP-1 levels ($p=0.049$) as compared to patients who had MI but had no family history

Interestingly, CAD is a multifactorial disease occurring from a complex interactions between genes and environment (25). Independent of established risk factors such as hypertension and elevated blood lipid levels, CAD in a first-degree relative confers an increase in risk of cardiovascular disease (26, 27). In a nationwide cohort study by Ran the et al using Danish national registers, , 4.4 million personsborn between 1930 and 1992 were followed for 104 million person-years, and 128,384 incident MIs were identified between 1930 and 1992. An incidence rate ratio (IRRs) was calculated for MIin 1, 2 or 3 first-degree relatives were 1.46, 2.38 and 3.58, respectively. Corresponding estimates for second-degree relatives were 1.17, 1.87 and 2.18. A history of MI in combinations of first and second-degree relatives increased risks 1.8- to 7- fold in middle-aged persons (28). Genetic predilection of CAD can be attributed to certain gene polymorphisms. In a meta analysis published in 2013 which included eleven case–control studies with a total 2325 MI patients and 6310 healthy controls , MCP-1-2518A>G polymorphism was implicated to be a potential risk factor for MI, especially among Asian populations.(29). In the Framingham Heart Study Offspring Cohort, higher circulating MCP-1 levels and a greater risk of MI was seen in persons with MCP-1-2578G allele (30).Another common genetic variant is the presence of isoleucine at position 64 instead of valine in CCR2. Deleterious effect of this 64I mutation was seen in a study where in patients aged 65 years or younger, the mutation was associated with myocardial infarction or reduced left ventricular function (31). However, the effect of this mutation on the risk of CAD is uncertain with a protective role of this polymorphism seen in healthy subjects with a family history of heart disease with two copies of the Ile allele due to decreased chances of coronary artery calcification (32).

MCP -1 levels are higher in CAD patients esp with acute coronary syndrome like MI than in healthy controls (33, 34). In the present study ,patients with recurrent MI had higher serum levels of MCP-1 compared to patients with first time MI though the difference was not statistically significant (p= 0.064) (Fig 2) .

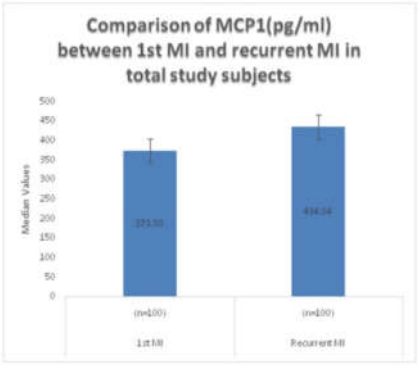

Fig 2 Patients with recurrent MI had higher serum levels of MCP-1 compared to patients with first time MI (p= 0.064)

Sustained inflammation after the first episode of MI could lead to persistent elevated levels of MCP-1 and the increased risk of major adverse cardiovascular events (MACEs) including recurrent acute coronary events. As is well known, healing requires a balanced inflammatory environment, and inflammation can act as a double edged sword. Although, monocytes and macrophages recruited by MCP-1 after MI scavenge tissue debris, stimulate angiogenesis and initiate collagen synthesis, these cells can also cause severe tissue damage by exaggerated secretion and release of proteases and oxygen radicals (35). Therefore, MCP-1 plays a major regulatory role in post infarction remodeling as an optimum amount of inflammatory monocytes recruitment, as governed by it, to sites of injury would result in better prognosis. It is also postulated that expression of MCP-1 might be carried to the late phase of acute coronary event in contrast to CRP which elevated in the acute phase only (36). Additional prognostic information in MI patients can be derived from serial measurement of MCP-1. (37). The A to Z trial suggested that risk stratification in both the initial and the chronic phases after an ACS can be done with the help of MCP-1 and MCP-1 >238 pg/ml remained independently associated with mortality and with each composite end point (38). Different mechanisms have been proposed for the adverse prognosis of patients with elevated MCP-1 levels (39). The higher baseline plasma MCP-1 may be due to increased expression of chemokines in the atherosclerotic lesion causing a more extensive disease or the amplified systemic activation of MCP-1 axis may result in greater prothrombotic effects leading to recurrent coronary events or, lastly, sustained elevated plasma MCP-1 levels may identify patients who exhibit a more exaggerated cardiac inflammatory reaction after MI. Hence, the inflammatory response after MI plays an important role in phagocytotic removal of dead cells and matrix debris from the infarcted region of the cardiac muscle. This inflammatory response is localized and transient, and is followed by clearing up of the inflammatory infiltrate and deposition of fibrous tissue (40). However, sustained inflammation after the acute event may result in adverse cardiac remodeling and secondary cardiac events.

CONCLUSION

MCP-1 has a key role in atherosclerosis right from initiation and progression of atherosclerotic lesion to plaque rupture and healing response following an acute coronary event. MCP-1 may be an encouraging biomarker for risk prediction in patients with coronary artery disease. It is essential to understand the nature of postinfarction inflammatory response incited by MCP-1 and other inflammatory mediators and offer treatment options for prophylaxis of secondary coronary events. MCP-1 and CCR2 can be effective future therapeutic target in the way of development of potent and specific antagonists against these in atherosclerotic disease and its complications.

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