Imbalances of Pro-inflammatory cytokines in myocardial infarction patients

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Abstract: To assess levels of Interleukin-1 β and CRP, in Diabetic and Non-diabetic Myocardial Infarction patients, prior to and post angioplasty. 200 patients were recruited in the study. MI patients between the age of 40 and 60 years. Patients came to NICVD with complaints of chest pain, positive Troponin T test and ECG was the confirmatory test for MI. They were divided into 2 groups 100 patients each. First group comprised of MI patients without DMT-II and second group comprised of MI patients with DMT-II. Serum triglycerides, cholesterol, LDL and HDL, FBS, by enzymatic kits, Insulin by RIA. HbA1C, Interleukin-1 β and CRP by ELIZA. Interleukin1β and CRP were significantly higher (P<0.001) in patients at the time of the infarction, prior to angioplasty as compared post angioplasty levels in both groups, which indicate their importance in development of ischemia and MI. FBS and Insulin were significantly higher (P<0.001), while HDL and HbA1C were significantly lower (P<0.001) in MI without DMT-II when compared to MI with DMT-II. BMI, SBP pressure were significantly higher (P<0.001) in MI patients with DMT-II when compared with MI patients without DMT-II. Interleukin1β and CRP were found to be significantly higher prior to angioplasty as compared to post angioplasty levels in both groups which confirms their role in development of ischemia and MI.

Keywords: Interleukin, myocardial infarction, diabetes mellitus, coronary angioplasty, C reactive protein.

INTRODUCTION

Interleukin-1β

The family of Interleukin 1(IL-1 *β)* comprises of four proteins which share sequence homology: IL-1*α*, IL-1*β*, IL-1receptor antagonist, and IL-18 (Dinarello *et al*., 1997). Immunore activity of IL-1*β has been* found in monocytes, macrophage, EC, and VSMC in human as well as in experimental atherosclerotic plaque; it is produced by EC, VSMC, macrophage and monocytes.

IL-1*β* is strongly pro-inflammatory for multiple cell types as it initiates expression of other inflammatory cytokines; it is induced by pro-inflammatory stimuli, like TNF*α* (Chamberlain *et al*., 2006; Tedgui *et al*., 2006). IL- 1*β* facilitates extravagation in early lesion formation by increasing leukocyte/EC interactions (Bevilacqua *et al*., 2011). It also induces cytokine expression in every cell present in the lesion autocrine and paracrine. It not only initiates but maintains local inflammatory response.

IL-1α and IL-1β correlate with progression of atherosclerotic plaques in humans; the expression in healthy coronary arteries is minimal, increased in atherosclerotic plaques, and high in complicated plaques (Dewberry *et al*., 2000). Inhibition is seen with the treatment of IL-1 blockers in progression of atherosclerosis (Bhaskar *et al*., 2011). Direct effects of IL-1β are seen in insulin resistance (Donath *et al*., 2011), thrombosis (Bevilacqua *et al*., 1984) and metabolic derangements in obesity (Chamberlain *et al*., 2009). As IL-1β direct plasma level determination is difficult, only few studies have shown increased levels of IL-1β in patients with atherosclerotic events (Ikonomidis *et al*., 1999; Saitoh *et al*., 2000). Prognosis after acute coronary syndromes IL-1β levels were not favorable (Correia *et al*., 2010, Orn *et al*., 2010)

Hwang *et al* suggested that IL-1beta neutralizes the acute phase of MI which is caused by cardiac rupture and thus have a protective role. (Hwang *et al* 2001. Reduced fatty streak area was seen in ApoE mice that were given a decoy infusion of IL-1 receptor (Elhage *et al*., 1998) Increased macrophage infiltrate with marked increased lesion area was seen in ApoE double knockout mice (Merhi-Soussi *et al*., 2005). A 30% decrease in atherosclerosis was seen in IL-1β/ApoE double knockout mice (Kirii *et al*., 2003). A therapy given to rheumatoid arthritis patients who included IL-1 neutralization showed beneficial symptoms like delaying the progression of the disease and joint destruction. In post-infarction cardiac remodeling and heart failure the emerging role of IL-1 family has been shown by the recent evidences (Nam *et al*., 2010). Pilot studies, preclinical models and observation data have suggested, a beneficial role of IL-1 blockade in a variety of pathologic processes including

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atherosclerosis, atherothrombosis, acute myocardial infarction, heart failure, and pericarditis. Pilot studies have shown promising safety and efficacy signals and a large cytokine inhibition study is ongoing to test IL-1β blockade in secondary prevention of patients with acute myocardial infarction (Ridker *et al*., 2010).

C-reactive protein

C-reactive protein (CRP) is an acute phase protein that is produced by stimulation of pro-inflammatory cytokines in the liver (Packard *et al*., 2000). It is strongly associated with cardiovascular risk (Boekholdt *et al*., 2006). In heart diseases it is a valuable tool to see the status of inflammation in patients because ease of measurement and the availability of the method. Numerous studies have shown both low- and high-sensitivity CRP to be associated with heart failure. Studies have shown high CRP levels in the elderly who prone to develop heart failure (Berton *et al*., 2003; Yin *et al*., 2004; Chirinos *et al*., 2005; Cesari *et al*., 2003).

A study that involved 4691 subjects from the general population, it was found that the relative risk of hospital admission for HF was twofold in those whose CRP levels were above 3 mg/L (Engstrom *et al*., 2009). It is seen in a study that there is an association between CRP and the stage of HF and it claims that CRP levels predict the probability of readmission to hospital due to deterioration in the functional stage of HF (Yin W-H*et al*., 2004; Alonso-Martínez *et al*., 2002). Some studies have found a stronger correlation between CRP and left ventricular ejection fraction and others have found no statistically significance between them (Berton *et al*., 2003; Yin *et al*., 2004; Alonso-Martínez *et al*., 2002). C-reactive proteins concentrations are of prognostic significance in unstable angina have been showed in a recent study (Liuzzo *et al*., 1994).

Objective of the study

To determine the role of pro-inflammatory cytokines Interleukin-1 β and CRP in Myocardial Infarction patients with and without Diabetes Mellitus Type II.

MATERIALS AND METHODS

Study design: Observational study

200 patients were recruited in the study they were MI patients between the age of 40 and 60 years. Patients came to NICVD with complaints of chest pain positive Troponin T test and ECG was the confirmatory test for MI (Inclusion criteria). Legal requirement was fulfilled by taking informed consent either from patient or his relatives before inducting them in the study. Ethical approval was taken from NICVD and Sindh University Jamshoro (Ref. No: ERC-11/2017). BMI was calculated after measuring Height and weight. Blood pressure and pulse was recorded. Exclusion criteria included person's suffering from hyperglycemic or hypoglycemia, diabetic ketoacidosis, inherited disorders of lipid and lipoprotein metabolism, deranged liver functions, Cerebrovascular accidents, and acute infections.

10 ml blood was taken after 10-12 hours fasting, after centrifugation Serum was collected and stored at –80°C for different parameters which included Serum Triglycerides, Serum Cholesterol, Serum HDL-Cholesterol, Fasting blood glucose which were assessed using automated enzymatic kits cobas integra provided by Merck & Roche. LDL-Cholesterol was calculated using Friedwald formula. Serum Insulin levels were done by radioimmunoassay (RIA) from Merck. HbA1C, Serum IL-1 β and CRP were measured by ELIZA with commercial kits from Gesendet: Donnerstag (DRG Instruments GmbH) Germany.

TOSHIBA Infinix 2000was used by consultant cardiologist to perform Angiography on MI patients after confirmation on the basis of history, signs and symptoms, ECG findings and positive Troponin T test.

STATISTICAL ANALYSIS

Data analysis was performed using the statistical package for the Social Sciences (SPSS ver.23). P value was determined by Students t test. $P<0.05$ was considered statistically significant. Gender and smoking were assessed by applying Chi Square test. Data is shown as mean and standard deviation. Sample size was determined by simple random sampling.

RESULTS

100 MI patient's diabetes and 100 MI patients with diabetes mellitus type II (DMT-II) were included in the study. table 1shows the baseline and physical parameter of MI patients with and without diabetes mellitus type II. Age, duration of diabetes and dystolic blood pressure was found to be non-significant between the two groups. BMI, systolic blood pressure were significantly higher ($P<0.001$) in MI patients with DMT-II when compared with MI patients without DMT-II. Gender and smoking were found to be non-significant among the two groups when Chi Square test was applied to them.

Table 2 Fasting blood sugar and insulin levels was significantly higher ($P<0.001$) in patients of MI with DMT-II when compared with MI without DMT-II. Triglycerides, Cholesterol and Low density lipoprotein were found non-significant in the two groups, while High density lipoprotein and Glycosylated hemoglobin were significantly lower ($P<0.001$) in MI without DMT-II when compared to MI with DMT-II.

Table 1: Baseline Characteristics of Patients n=200

	Myocardial Infarction N (100)	Myocardial Infarction with Diabetes Mellitus Type II N(100)	P-Value
Gender (Male/Female)	68 / 32	63 / 37	0.457
Age (Years)	55 ± 4	56 ± 3	0.079
Height (m)	1.55 ± 0.01	1.54 ± 0.01	0.201
Weight (Kg)	68.22 ± 1.29	70.47 ± 2.49	0.001
Body Mass Index (BMI) (kg/m^2)	27.57 ± 2.2	29.47 ± 4.71	0.001
Duration of Diabetes Mellitus (Years)	-	12 ± 3	-
Smoking	20	25	0.404
Systolic Blood Pressure (mmHg)	130 ± 5	129 ± 8	0.001
Diastolic Blood Pressure (mmHg)	80 ± 4	81 ± 6	0.012

Values are expressed as mean and standard Deviation (SD). Student's t test is applied to obtain significance P-<0.001

Table 2: Biochemical Parameter of patients in relation to Blood Glucose and Blood lipid Levels n=200

	Myocardial Infarction	Myocardial Infarction with Diabetes Mellitus Type II	P-Value
Fasting Blood Glucose (mg/dl)	80 ± 4	132 ± 16	0.001
HbA1C (%)	5 ± 0.70	7 ± 0.81	0.001
Fasting Insulin (µIU/mL)	11 ± 2	19 ± 4	0.001
Serum Triglycerides (mg/dl)	190 ± 25	185 ± 26	0.172
Serum Total Cholesterol (mg/dl)	204 ± 22	196 ± 24	0.013
Serum LDL Cholesterol (mg/dl)	147 ± 30	144 ± 37	0.557
Serum HDL Cholesterol (mg/dl)	24 ± 5	27 ± 7	0.001

Table 3: Levels of Inflammatory Cytokines in Myocardial Infarction patient's pre and post angioplasty n=100

	Pre angioplasty	Post angioplasty	P-Value
Interleukin-1β (pg/ml)	5.81 ± 0.58	3.06 ± 0.53	0.001
C-reactive protein (mg/l)	32.66 ± 7.83	1.85 ± 0.28	0.001

Values are expressed as mean and standard Deviation (SD). Student's t test is applied to obtain significance P-<0.001

Table 4: Levels of Inflammatory Cytokines in Myocardial Infarction patients with Diabetes Mellitus Type II, pre and post angioplasty n=100

	Pre angioplasty	Post angioplasty	P-Value
Interleukin-1β (pg/ml)	6.46 ± 0.98	3.60 ± 0.57	0.001
C-reactive protein (mg/l)	38.25 ± 7.92	2.57 ± 1.08	0.001

Values are expressed as mean and standard Deviation (SD). Student's t test is applied to obtain significance P-<0.001

Table 3 In MI patients at the time of the infarction, prior to angioplasty the pro-inflammatory cytokines Interleukin1 β and CRP were significantly higher (P<0.001) as compared to levels which were done after the angioplasty which indicate their role in ischemia and MI.

Table 4 In MI patients with DMT-II, the levels of pro-inflammatory cytokines Interleukin1 β and CRP were found to be significantly higher (P<0.001) prior to angioplasty when compared with post angioplasty levels which also indicates that they play an important role in development of ischemia which leads to MI.

DISCUSSION

Serum interleukin 1-beta

It is found that Serum Interleukin 1-beta (IL-1β) concentrations in diabetic and non-diabetic Myocardial Infarction (MI) patients were raised at the time of Ischemia/MI as compared to the levels done after the inflammation has subsided that is post angioplasty. Matsumori *et al* stated that in healthy controls and the patients who completely recovered after MI the IL-1β concentrations were undetectable (Matsumori *et al*., 1994). In early course of MI, IL-1β plays as important mediator in inflammatory process (Gruzdeva *et al*., 2017). In early phase acute MI, IL-1 receptor antagonist have

been detected (Latini *et al*., 1994). In our study the raised levels of IL-1β in patients prior to and post angioplasty are related to pro-inflammatory response at the time of ischemia and reperfusion. IL-1β and coronary artery disease leading to atherosclerosis is linked by considerable evidence, is due to the inflammation in vascular wall (Ross *et al*., 1986). The raised active inflammatory response in vascular wall during and after ischemia. Endothelial dysfunction in atherosclerosis is attributed to impaired production/secretion of vasodilators such as endothelial derived relaxing factor Nitric Oxide (NO) (Ishizaka *et al*., 1991). It is of great interest that the enzyme responsible for NO production the NO- Synthase, its metabolism is regulated by IL-1β (Tsujino *et al*., 1994; Cunha *et al*., 1994, Szabo *et al*., 1993). The atherogenesis which leads to high morbidity and mortality rates can be controlled or somewhat inhibited by using IL-1β receptor antagonist (Dinarello *et al*., 1993, Alexander *et al*., 1992) which in turns reduces the vascular inflammation in atherogenesis and thus plays as a protective role in MI (Hamsten *et al*., 1995, Brown *et al*., 1990, Maulik *et al*., 1993).

More in-depth studies which also involve histopathological evidences are needed to link IL-1β concentrations and ischemia/ MI. It can give an insight to the role of IL-1β and Ischemic Heart Disease (IHD) (Van Tassell *et al*., 2017). In sub-acute phase of AMI IL-1β loss of viable myocardium which promotes cardiac dilation and dysfunction and suppresses cardiac contractility and β-adrenergic receptor responsiveness. When IL-1β Inhibitors given during AMI they tend to have the potential to prevent adverse cardiac remodeling and/or heart failure (Toldo *et al*., 2017). In future serum IL-1β levels can/will be used for the diagnosis of IHD patients.

C-reactive protein

An increase level in markers of inflammation acute phase proteins and cytokines play important role in inflammatory processes by determining plaque stability, destabilization and rupture of atherosclerotic plaques, leading to acute cardiovascular events (Nikolaos *et al*., 2015). For the prediction of CHD and as a causal factor C-reactive protein (CRP), a prototype marker of the inflammatory process, is the most studied (Shrivastava *et al*., 2015). CRP can be measured inexpensively with available high-sensitivity assays it has no diurnal variation, levels are stable over long periods, have shown specificity in terms of predicting the risk of CHD (Devaki *et al*., 2011). CRP might have a role in the genesis of atherosclerotic lesion as it reduces the expression of nitric oxide (NO) synthase and prostacyclin synthase, binds LDL-C and promotes its uptake by macrophages, which is a key step in atherogenesis. CRP regulates the expression of adhesion molecules on endothelial cell (EC) (Mehta *et al*., 2006). Shrivastava *et al*., 2015 suggest that those with stable and unstable angina, presenting to emergency rooms with acute coronary syndrome (ACS) and those undergoing percutaneous angioplasty, CRP levels have shown to predict risk of both recurrent ischemia and death among these patients (Nikolaos *et al*., 2015; Greenland *et al*., 2010).

Our study focused on the levels of CRP in diabetic and non-diabetic Myocardial Infarction patients who had an episode of ischemia/MI and it was found that there was significantly rise in the levels at the time of ischemia before the angioplasty was done and the levels subsided after angioplasty was done and the inflammation got subsided, which confirms the role of CRP in atherogenesis as well as ischemic heart disease.

CONCLUSION

The increase in the levels of pro-inflammatory cytokines IL-1β and CRP levels in Myocardial Infarction patients with and without diabetes mellitus type II at the time of ischemia and decrease after the angioplasty was done and the inflammation got subsided shows that these cytokines play an important role in the cascade of ischemia/ Myocardial Infarction and rupture of plaque.

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