The role of Interleukin 6 , C Reactive Protein ,C3and C4 Complement in Immunopathogenesis of Myocardial Infarction

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Abstract

Background: Coronary artery disease is the leading cause of premature death in the developed world and is estimated to become, by 2020, the major cause of death worldwide.
Objective: To Evaluate the role of interleukin 6 and acute phase proteins in immunopathogenesis of myocardial infarction.
Patients and Methods: This study was conducted in Baquba Teaching Hospital in Diyala province .Ninety blood sample were collected from patients with myocardial infarction, 62 (68.9%)were males and 28 (31.1%) were females with age range (25-90) years, control group (35) patient, a males were 28 (77.14%) , and females were 8 (22.86%) with age range (25-70) years.
Results: The results showed levels of Interlukine-6 was higher in patients (47.44 ± 30.50) pg / ml than control (37.13 ± 12.08) pg / ml with no significant difference and the positivity of C-reactive protein in patient group was (81.3%) than control group was (0%) ,with highly significant different , the level of C3 and C4 in present study was lower in patient than control group.The C3 complement level was (112.88) pg / ml which is lower than control group (121.48 ±) pg / ml ,while C4 level was (19.73) pg / ml also lower than control group (26.81) pg / ml and significant difference was noticed among C4 .
Conclusion: We concluded that there is high level of IL-6 in patients with myocardial infarction and significantly high levels of C-Reactive Protein in patients of Myocardial infarction while showed there are low concentration levels of C3 and C4complement in patients with myocardial infarction**.**
Keywords: Myocardial Infarction , Interlukine-6 , CRP , complement C3 and C4

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Introduction

Myocardial ischemia is a condition characterized by inadequate myocardial perfusion ,may result from an increase in myocardial oxygen demand in the setting of a flow-limiting coronary stenosis (reduced flow reserve, the predominant mechanism in

stable angina) or a primary reduction in coronary blood flow due to thrombosis or vasoconstriction [1] .Coronary artery disease (CAD) is the leading cause of premature death in the developed world and is estimated to become, by 2020, the major cause of death worldwide[2]. Almost all myocardial infarction result from coronary atherosclerosis, generally with superimposed coronary thrombosis[3].

Interlukin-6 is the proinflammatory cytokines that produced from different cells such as fibroblast , mononuclear cells , mast cells and T lymphocytes cells [4] , and a cording to studies , IL-6 contributes to the development of infarct size in the early phase of reperfusion; this contribution independent on neutrophil influx, IL-1β and TNFα, tissue factor and fibrin [5]. C-Reactive Protein CRP is the first acute phase proteins , and is immunogenic protein that synthesis in liver from hepatocytes. This protein used in investigation on several diseases such as acute hepatitis , bacterial endocarditis and myocardial infarction , in high concentrations of this protein give as evidence of acute inflammation [6] and CRP leads to activation complement system through the classical pathway , lead to opsonization of pathogens and damaged cells[7].

The potential atherogenic role of the complement system, a main effector arm of immunity and inflammation, remains to be determined. The complement system interact with one another in 3 activation cascades known as the classic, the alternative, and the lectin pathways[8] , (C3) is constitute (70)%

from complements proteins and consider more complement proteins concentration in serum, decrease concentration of C3 protein may cause repeated bacterial infections and acute inflammation[9]. Patients deficient in C3 protein are suffering from repeated bacterial infection [10]. Aim of this study was to investigate the possible role of CRP, IL 6, and complement C3, C4 as a candidate biomarker in patients with myocardial infarction.

Patients and Methods

The present study was conducted during period from 1/5/2015 to 1/5/2016 . Ninety blood samples was collected from patients with acute myocardial infarction who were admitted to cardiac care unit at Baquba Teaching Hospital in Diyala province, the number of male [62] and female [28] within the age range between (25-95) years. Also collected [36] blood sample from healthy people and use them as a control group , from 36 control group a [28] were male and [8]were female within age range between (25-70) years. The study was approved from the ethics committee of the Institute and informed consent were obtained from patients.

We aspirated a (5ml) of venous blood from patients and healthy people included in the study , mediated by sterile syringes and region with draw the sterilized by (70%) alcohol or Dettol , after the separation of serum by using centrifuge at rate of 3000 r/min for [10] minutes. The separated serum distribute into eppendrof tube in equal amounts (500µl) and these tubes keep in

deep freeze at temperature (-80C°) until use , each eppendrof tube used to avoid freezing and thawing of the model. Concentrations of (IL-6) determined by (ELISA) technique (IL-6 Human ELISA Kit, catalog number: KHC0061) according to the manufacturer instructions   , also serum had been tested for C-reactive protein by high sensitive Enzyme linked Immunosorbent Assay (ELISA kit, BioCheck, Inc 323) and according to manufacturer instructions , Radial Immunodiffusion assay was used for quantitative determination of C3 and C4 complement using Single radial immunodiffusion test. It was done according to manufacturer instruction (Sanofi diagnostic, Pasteur, France).

Statistical analysis

Continuous variables are reported as mean ± standard deviation. Univariate analysis was performed to determine the association between these markers and with myocardial infarction. A P-value < 0.05 was considered to be statistically significant, with a 95% confidence interval (CI). Calculations were done using SPSS version 20(39).

Results

Estimation of (IL-6)

There is high level of (IL-6) in patients with myocardial infarction (47.4±30.5) pg/ml than control group (37.13±12.08) pg/ml and without statistical significant different (p=0.23).

Table (1): Showed comparison level of (IL-6) between study groups.

Pg/ml		Study group		P-value
		Control	Patients	
Serum IL-6	Mean	37.13	47.44	0.23 NS
	SD	12.08	30.50	

Estimation of C-Reactive

Protein CRP was positive in (61) patients of MI from (75) patient and percentage (81.3%) . so

results of current study was highly significant between study groups (p=0.001).

Table (2): show positivity of CRP within study groups.

		Study group	
		Control	Patients
CRP	Negative	15	14
	%	100%	18.7%
	Positive	0	61
	%	0%	81.3%
Total		15	75

Complement system C3 and C4 levels of

Which showed there is low concentration of C3 and C4 in patients with myocardial infarction, the C3 level was (112.48) mg/dl compared with control groups (121.48) mg/dl with no significant differences (p=0.3) , while the result showed low concentration of C4 in patients (19.73) mg/dl compared to control group (26.81) mg/dl with high significant different (p=≤0.0001).

Table (3): Estimate concentration levels of C3 and C4 between study groups.

Mg/Dl		Study group		P value
		Control	Patients	
C3	Mean	121.48	112.88	0.3 NS
	SD	29.484	44.58	
C4	Mean	26.81	19.73	0.001***
	SD	8.677	6.092	

*NS=No significant
** high significant

Discussion

Estimation of of (IL-6)

Results of our study showed high level of (IL-6) in patients with myocardial infarction without statistical significant differences. The results of our study were comparable with the study done in Iraq by Ibrahim et al.at 2012 which showed high level of (IL-6) concentration in patients of myocardial infarction with high significant differences (p=< 0.001) [11].Our study similar to another study done in Iraq by Al-Najay and Al-Jofy , 2009. showed the levels of (IL-6) increase significantly with patients of myocardial infarction[12].

Also our study agree by another many study ,such us Al-Ghurabie (2012) showed (IL-6) levels increase in patients of myocardial infarction that the IL6 increase the inflammatory process and thrombosis [13]. Also Nunez l., study at (2012) showed the people that suffer from myocardial infarction and infection with cytomegalovirus

have high level of (IL-6) that associated with higher mortality[14] ,and another study done by Abdulkarim showed the levels of (IL-6) increase with myocardial infarction , and there is a strong correlation with coronary angiography , that making the (IL-6) risk factor and good predictor for coronary artery diseases[15].

Patients with acute myocardial infarction and infected with cytomegalovirus have high levels of (IL-6) and play role and acceleration of cardiac damage[16] , Al-Ghurabie study showed the (IL-6) is a pro inflammatory cytokine can be stimulate heart damage during acute heart diseases[13].

Debrunner study and Su study , also showed the (IL-6) had significant correlation in patients with heart and blood vessels diseases and showed the high levels of (IL-6) in patients of myocardial infarction[17] [18] , therefore the IL-6 can be used as predictor

factor for diagnosis myocardial infarction disease [19].

Estimation of C - reactive protein

Our study showed positive correlation of CRP within study group , positivity of CRP in patients of MI was (61) from (75) patient and percentage (81.3%) . so results of current study was significant between study groups (p=0.001).

Results of current study was agree with study of Ibrahim, (2012) that showed significantly high levels of CRP in patients of MI (p=0.001) [11] , the high levels of CRP can be used as predictor factor for coronary artery disease in patients with MI and unstable angina, also this rise can be lead to restenosis of artery after it has opened with cardiac catheterization[20].

The study done by Al-Najy , Al-Jofy and Abdulrazzaq revealed that high concentration of CRP in patients with MI with significant (p≤0.001)(12,21). Also Greenland, 2010 showed in acute MI and positivity of CRP is associated with several diseases such as (coronary heart diseases) [22]. Smimanek a. , 2011) study showed that CRP is inflammatory marker associated with development of heart diseases , atherosclrosis and mortality [23].

Many another studies like Mahajan, Al-Gurabei, Al-Sadi Calabro and zaikas studies mention the levels of CRP increase largely in acute MI and showed the CRP may play large role in modified inflammatory immune response after acute myocardial infarction and other forms of tissue injuries , and this refer the activation of complement system

and thus tissue damage, so CRP can be activation complement system in damage of blood vessels . all these studies confirmed and agree with our study showed that high levels of CRP in coronary artery diseases([24,5,25,26,27,28].

Complement system C3 and C4

Our study showed there is low concentration levels of C3 and C4 in patients with myocardial infarction, with no significant differencs (p=0.3) , while the result showed low concentration of C4 in patients high significant different (p=≤0.0001) . Our study agree with study of Paakkahen, (2009) that show decrease level of C3 its not effected in patients of acute myocardial infarction[29].

While another two studies done by (Delves, , 2006) and(Jinrong, 2006)[31]. are showed the activation of complement one cause in pathogenesis of myocardial infarction and Synthesize C3 and C4 in infarcted heart , although it synthesize in live and inflammatory cells[30,31].

Our study not agree with Hiad , study at 2011was mention the C3 complement concentration was high in most patients of acute coronary syndrome in first [24] hour of infarction[27] , also not agree with IItumur, study (2005) and Micheal, 2002 showed in there study , that there is a marked increase in level of C3 in patients that suffering from MI they said that the C3 may be product through infarction cardiac cell[32,33].

While Delves, (2006). Mention in his study the activation of complement may be lead to inflamation of heart muscle during formation

of membrane attack complex and generate (anaphylatoxins) [30]   , so non-significant different may be because of the high level C3 is locally in necrotic heart muscle. Onte study showed the C3 play important role in systemic inflammations so C3 increase in patients that suffering from heart diseases and C3 associated with tissue damage in site of infracted heart so these two above studies agree with our study[34], according prevalence studies the C3 and C4 are inflammatory factor for predict for coronary artery disease , that refer to monitoring high and low levels of C3 and C4 with risk factor[35].

While Lim and Monowar study mentioned that the levels of C3 and C4 increase significantly in serum of acute MI patients comparable to control and the cause of these increased is due to synthesize complement components or adequate regulation , moreover , searcher pointed in his study the activation complement system happen after attack with MI and that was associated with inflammatory response and acute phase and degree of activation system may be associated with size of necrosis heart muscle , and decrease these levels in final days of MI. Increase concentration C3 play direct role in increase proliferation of vascular smooth muscle cell [36,37, 38].

Conclusions

We concluded that there is high level of IL-6 in patients with myocardial infarction and significantly high levels of C-Reactive Protein in patients of Myocardial infaection while showed there are low concentration

levels of C3 and C4complement in patients with myocardial infarction.

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