Evaluation of Certain Acute Phase Reactants in Patients with Acute Myocardial Infarction

Noaman Abdullateef Abdulrazzaq*, Abdulbasit Insief Jassim , Ali Ibrahim Kadhum*****

ABSTRACT:

BACKGROUND :

Acute myocardial infarction (AMI) is an important clinical condition which is associated with a significant inflammatory changes that result in acute-phase responses. Significantly elevated concentrations of cytokines and other acute phase reactants are the major events that accompanied such condition. Our aim was to evaluate certain acute phase reactants : Interleukin-6 (IL-6) , C-Reactive Protein (CRP) and plasma fibrinogen in patients with AMI.

OBJECTIVE:

This study was focused on the evaluation of certain acute phase reactants : Interleukin-6 (IL-6) , C-Reactive Protein (CRP) and plasma fibrinogen in patients with AMI.

PATIENTS AND METHODS:

Thirty patients from Baghdad city with AMI were included between July 2011 and January 2012 : 21 males and 9 females, their ages range between 40 – 73 years. Thirty healthy subjects (16 males, 14 females), age matched with patients as a comparative group were included. Both groups were investigated for IL-6 , CRP , and plasma fibrinogen levels.

RESULTS :

IL-6 concentrations were found to be significantly higher with (P value : 0.0001) –table 1- in patients with AMI) than in control subjects. CRP concentrations were also found to be significantly higher with (P value : 0.0001) in patients with AMI than in control subjects. plasma fibrinogen level was significantly higher with (P value : 0.0001) in patients with AMI than in control subjects.

CONCLUSION :

The study revealed a significant elevation in IL-6 , CRP concentrations and plasma fibrinogen level in patients with AMI.

KEY WORDS : interleukin-6 , c-reactive protein , fibrinogen.

INTRODUCTION :

The acute phase response is part of the body's reaction to injury or infection. It is associated with alterations in the metabolism of many organs as well as changes in the plasma concentrations of various acute- phase proteins.[1,2] Interleukin 6 is a multifunctional protein produced by lymphoid and non-lymphoid cells and by normal and transformed cells, including T cells, monocyte/macrophages, fibroblasts, hepatocytes, vascular endothelial cells. [3] There has been considerable interest in the possible etiological role of inflammation in vascular disease. Interleukin-6 (IL-6) is one of a number of inflammatory markers that have been studied. [4] In addition to the association with CHD, IL-6 levels were also strongly associated with a number of established risk factors and other inflammatory markers. [5] Many prospective studies have shown an associations between CHD events (MI and CHD death) and C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, von Willebrand factor (vWF), fibrin D-dimer and tissue plasminogen activator antigen (t-PA) in both middle-aged and older populations. There is mounting evidence that inflammation plays a role in the development of coronary heart disease (CHD). Observations have been made linking the presence of infections in the vessel wall with atherosclerosis, and epidemiological data also implicate infection in remote sites in the etiology of CHD. [6] C-Reactive Protein (CRP) is an acute phase protein, originally identified and named for its ability to precipitate the C-polysaccharide of pneumococcus in the presence of calcium1. It is the prototypic acute phase reactant whose presence in plasma or serum serves as a useful

*Biochemistry Department ,Central Public Health Laboratories.
**Hematology Department ,Central Public Health Laboratories.
***Department ,Al Mansour Medical Technical Institute.

laboratory indicator of systemic inflammatory disease. [7]

High sensitivity CRP (hs-CRP) levels have been proved to be strongly predictive of cardiovascular events and potentially associated with the severity of coronary atherosclerosis. Utility of this biomarker for cardiovascular risk stratification in populations with and without established cardiovascular disease is supported by strong evidence. In particular, it was shown that survival rate following percutaneous coronary intervention in patients with angina was significantly low in those with high CRP levels. [8] Studies have shown that CRP concentration in serum is also elevate in ACS compared to stable angina or vasospastic angina. Elevated CRP is associated with increased cardiac morbidity. [9,10]

Plasma fibrinogen is one of the major acute phase proteins and several prospective studies provided evidence that high fibrinogen level is an independent predictor of cardiovascular complications and that fibrinogen may play an important role in the pathogenesis of atherosclerosis. In men, increased fibrinogen was significantly associated with coronary heart disease (CHD) events, stroke and transient ischemic attacks, also there is an evidence that plasma fibrinogen is associated with an excess risk of CHD in women. The independent association of fibrinogen with cardiovascular mortality was at least as strong as the association of such deaths with blood cholesterol. [11] Stout and Crowford have shown seasonal variation in plasma fibrinogen in the elderly and suggested that the greater concentration in winter (due to the increased incidence of respiratory infections) could increase the risk of (CVD). [12]

The role of hypercoagulability and plasma fibrinogen has been suspected for many years, and has recently been documented by experimental and clinical evidence : human gelatinous and fibrous are plaques rich in fibrinogen which is involved in mechanisms (platelet aggregation, endothelia cell injury, and plasma viscosity) that play a central role in the formation of thrombi; and thrombosis is major determinant of myocardial ischemia. [13,14]

PATIENTS AND METHODS :

This prospective study was done for the period between July 2011 and January 2012 . Thirty patients from Ibn Alnafees teaching hospital were included : 21 males and 9 females, their ages range between 40 – 73 years. All patients had documented acute myocardial infarction which diagnosed clinically with significant electrocadiographic (E.C.G.) changes showing AMI Thirty healthy subjects (16 males, 14 females), age matched with patients were included as control group. All patients and control subjects were investigated to quantify IL-6 , CRP and plasma fibrinogen in their serum. The Clauss method was used for quantifying plasma fibrinogen (fortress diagnostics). The High Sensitive CRP Enzyme Immunoassay (hsCRP ELISA) method was used for quantitative determination of CRP concentration (DRG International Inc.,USA) . The quantitative determination of IL-6 method is based on ELISA (a one immunological step sandwich type assay - Immunotech SAS,France-) Statistical Analysis : The student T-Test was used for statistical tests. Results were expressed as the mean ± SEM , and were considered to be statistically significant when the value of P was less than 0.05.

RESULTS :

IL-6 concentrations were significantly higher in patients with AMI than in control subjects (as shown in table -1-)

Table 1: IL-6 (pg / ml) in normal control subjects and in patients with AMI.
M = Mean , SEM = Std. Error of Mean.

Test	Patients	Control	P value
	M ± SEM	M ± SEM	
IL-6	162.33±26.78	6.77±0.81	0.0001*

* = Significant using student t-test for two independent means at 0.05 level of significance.

CRP concentrations were significantly higher in patients with AMI than in control subjects (as shown in table -2-) .

Table 2: CRP (mg / L) in normal control subjects and in patients with AMI.

Test	Patients	Control	P value
	M ± SEM	M ± SEM	
CRP	13.84±0.46	4.28±0.53	0.0001*

M = Mean , SEM = Std. Error of Mean.
* = Significant using student t-test for two independent means at 0.05 level of significance.

Plasma fibrinogen levels were significantly higher in patients with AMI than in control subjects (as shown in table -3-) .

Table 3: Plasma fibrinogen (g / L) in normal control subjects and in patients with AMI.

Test	Patients	Control	P value
	M ± SEM	M ± SEM	
Plasma fibrinogen	4.56±0.18	2.74±0.12	0.0001*

M = Mean , SEM = Std. Error of Mean.
* = Significant using student t-test for two independent means at 0.05 level of significance.

DISCUSSION :

IL-6 was significantly higher in patients with AMI than in control subjects (table -1-). Other studies on patients with AMI had found the same results; (Dizdarevic L., et al) [15] , (Suzuki H., et al) [16] , (Moe K. , et al)[17] (Byrne C. , et al) [18]. IL-6 is a cytokine responsible for acute phase protein production by the liver and it is one of the important cytokines associated with response to inflammation [19,20] . It is the only cytokine that can stimulate the synthesis of all the acute phase proteins involved in the inflammatory responses [21]. Studies showed that IL-6 is the main endogenous mediators of acute phase response in patients with AMI and there is a strict relation between IL-6 elevation and the extent of myocardial tissue damage. [22]

The association of IL-6 with the risk of CHD including AMI was found to be similar in nature and magnitude to that of a number of major established determinants of vascular disease and studies demonstrated significant associations between long-term elevated circulating IL-6 levels and CHD risk in the population. [5,6,23]

As shown in table (2), CRP concentrations were significantly higher in patients with AMI than in control subjects and this results agree with that of other studies; (Ruckerl R. ,et al) [24] , (Byrne C. , et al) [18] and (Moe K. , et al) [17]. IL-6 and CRP have related roles in the inflammatory response : IL-6 induces CRP production in the liver by activating Janus Kinases. Signal transducers and activators of transcription subsequently switch on the CRP gene expression, leading to the production of CRP. [25] The CRP level certainly rises as a consequence of the inflammatory response to myocardial necrosis and some studies have reported significant correlations between CRP concentration and the size and extent of necrosis. [17] Also studies have demonstrated that the baseline CRP concentration can predict cardiovascular events. [6,23]

The result of this study showed that plasma fibrinogen level was significantly increased in the acute phase of AMI, table (3). Other studies on patients with AMI showed the same results; (Mircea P., et al) [26], (Tlaines A.P., et al) [27] and (Hoffmesiter H., et al). [28] Myocardial necrosis is considered to be a potential source of inflammation [29], and its accompanied by elevated levels of acute-phase reactants, which reflect the stimulation of hepatic production by circulating inflammatory mediators such as cytokines, especially IL-6. [20,29]

Fibrinogen is an acute phase protein and its synthesis in the acute phase response is related to the action of IL-6. [20,21,30] IL-6 is extremely important in regulation of fibrinogen levels, as there is an IL-6 responsive element in the promoter region of the β-fibrinogen gene. Synthesis of the β-chain is known to be rate-limiting step in fibrinogen synthesis. [21]

CONCLUSION :

This study revealed a significant elevation in IL-6 , CRP concentrations and plasma fibrinogen level in patients with AMI.

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