The Correlation Between Insulin ,IL-6 and CRP in Acute Myocardial Infarction

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ABSTRACT:

BACKGROUND:
Insulin is a hormone produced by the beta cells of the pancreas. Insulin is necessary for the uptake of glucose into all cells in the body other than the Brain. C reactive protein (CRP) is a main inflammatory factor that is produced by the liver during acute infection or inflammation and its concentration in plasma can increase as much as 1000-fold during injury and infection. Interleukin-6 (IL-6), a major regulatory proinflammatory cytokine, is produced by a variety of cells, including leukocytes, adipocytes, and endothelial cells, and acts on the liver to stimulate the production of a number of acute-phase proteins.

OBJECTIVE:
The present study was designed to examine the relationship between fasting plasma IL-6 and CRP concentrations and insulin action in acute myocardial infarction patients.

SUBJECTS AND METHODS:
The study included 50 patients with acute Myocardial infarction (AMI) and forty healthy subjects as control group. Levels of insulin, CRP and IL-6 were measured.

RESULTS:
The levels of insulin, IL-6 and CRP were significantly elevated in AMI patients with ($p<0.001$). There was positive correlation between insulin with CRP and IL-6 in acute myocardial infarction patients.

CONCLUSION:
The significant increase in insulin in AMI may be related to inflammation. Insulin positively correlated with inflammatory markers (CRP and IL-6).

KEY WORD: insulin , CRP, IL-6, acute myocardial infarction.

INTRODUCTION:

Insulin is a hormone produced by the beta cells of the pancreas. It is necessary for the uptake of glucose into all cells in the body other than the Brain[.(1)] C reactive protein (CRP) is a main inflammatory factor that is produced by the liver during acute infection or inflammation and its concentration in plasma can increase as much as 1000-fold during injury and infection [(2)]. CRP may be independent risk factor for chronic kidney disease in patients with type 2 diabetic. CRP level is significantly higher in the obese diabetes patients compared with the healthy normoglycemic controls [(3)]

Experimental evidence and some cross sectional data demonstrated that C-reactive protein as a sensitive physiological marker of subclinical systemic inflammation is associated with hyperglycemia, insulin resistance, and overt type 2 diabetic. [(4)] An association between plasma high-sensitivity C-reactive protein (CRP) concentrations and cardiovascular disease has been noted in both men and women. Understanding this association is of great importance because it may provide new insight into mechanisms of atherosclerosis or thrombotic events as well as leading to potential new prevention strategies or therapeutic interventions. Subsequent studies have demonstrated that CRP concentration is significantly related to various measures of body fat [(5,6,7)].

In this context, at least some of the studies reporting an association between obesity and CRP concentrations also described a relation between plasma CRP and fasting insulin concentrations(5), A surrogate measure of insulin

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resistance. Moreover, we have previously reported that improving insulin resistance with an insulin-sensitizing agent markedly reduced CRP concentrations in the absence of weight loss[8,9]

A body of evidence has accumulated over the past decade supporting the concept that insulin resistance and type 2 diabetes are related to a chronic, low-grade, inflammatory state. Cross-sectional studies in type 2 diabetic patients or in individuals with impaired glucose tolerance/impaired fasting glucose have shown that acute-phase markers are elevated in these subjects compared with non diabetic control subjects. Several studies have shown that proinflammatory cytokines and acute-phase reactants are correlated with clinical features of the metabolic syndrome, including measures of insulin resistance/plasma insulin concentration, BMI/waist circumference, and circulating triglyceride and HDL cholesterol concentration [10]

In addition, many prospective studies in different human populations have identified proinflammatory cytokines, acute-phase proteins, and several indirect markers of inflammation as predictors of type 2 diabetes and glucose disorders. [11]

Interleukin-6 (IL-6), a major regulatory proinflammatory cytokine, is produced by a variety of cells, including leukocytes, adipocytes, and endothelial cells, and acts on the liver to stimulate the production of a number of acute-phase proteins. Circulating IL-6 levels have been reported to be elevated in subjects with type 2 diabetes and to correlate with direct and indirect measures of insulin resistance . However, while the relationship between insulin resistance and circulating IL-6 levels is well established, there is little information on an independent association between plasma IL-6 levels and insulin secretion. [11] it is possible that the effects of IL-6 on pancreatic β-cell function are direct rather than mediated by inflammatory molecules partly, but not exclusively, regulated by IL-6.

SUBJECTS:

This study was performed during the period from December 2009 to April 2010. This study included fifty patients with Acute Myocardial Infarction (AMI) who admitted to Cardiac Care Unit (CCU) at Medical City Teaching Hospital and Ibn –ALbetar Hospital in Baghdad. Patients , with age range (20-78) years, were included in this study. Blood samples were taken from the patients after having thoroughly examined after exclusion of subjects with a history of previous AMI or diabetes mellitus or any chronic diseases. Control groups included forty age, sex and BMI matched.

Blood collection and laboratory analysis

From each patients and control, five ml of venous blood were aspirated from a suitable vein. Samples were collected between (8-9 A.M.) after 10 hours fast. Blood samples were transferred to plain tubes for storage to measure the insulin, IL-6 and CRP. The non heparinized blood in the plain tubes were left to clot and then centrifuged at 4000 rpm for 5 minutes to separate the serum and dispensed into tightly closed Eppendorf tubes in 1.0 ml and stored at -20 C° until assayed. Each serum sample was analyzed for urea and creatinin to excluded kidney diseases. insulin, IL-6 and CRP were measured by using ELISA kits from United States Biological Company.

Statistical analysis

Statistical analysis was performed by statisticians with the SPSS 15.01 Statistical Package for Social Sciences and also Excel 2003. Data analysis was done using chi- square test for tables with frequencies, while we used independent sample t-test for tables with means and standard deviations. p value of ≤ 0.05 was used as the level of significance. Correlation coefficient used to find the correlation between studied markers by using Pearson correlation. Descriptive statistics for the clinical and laboratory results were formulated as mean and standard error.

RESULTS:

Serum levels of Insulin, IL-6 and CRP were compared between the studied groups as in table (1). The patients with AMI were found to have significantly higher serum of IL-6 and CRP and insulin   with   (p<0.001)

Table 1: The comparison between groups for (insulin,IL-6 and CRP) in studies group.

parameters	Female patients Mean±SR NO.=16	Female Control Mean±SR NO.=16	P-value	Male Patient Mean±SR NO.=24	Male Control Mean±SR NO=34	p -value	Total Patients Mean±SR N0.=50	Total Control Mean±SR N0.40	P- value
Age Years	61.70 ±10.19	60.18 ±9.938	0.523	53.37 ±12.20	54.043 ±9.148	0.620	56.26 ±12.11	56.51 ±9.19	0.916
BMI=(weight/(height)^2) Kg/m2	26.97 ±2.99	26.62 ±3.65	0.803	29.03 ±5.28	29.1 ±2.7	0.943	28.19 ±4.88	28.47 ±3.03	0.763
IL-6 Pg/ml	87.64 ±8.70	33.946 ±7.158	<0.001	84.97 ±2.34	32.567 ±4.229	<0.001	85.89 ±3.35	33.13 ±8.06	<0.001
CRP mg/L	23.72 ±5.08	15.192 ±2.799	<0.001	20.60 ±6.76	10.825 ±5.588	<0.001	22.34 ±6.26	12.75 ±1.29	<0.001
Insulin ulU/ml	71.99 ±6.05	29.792 ±8.309	<0.001	71.74 ±9.70	34.092 ±7.980	<0.001	71.83 ±11.09	32.39 ±4.50	<0.001
Glucose mg/dl	135.94 ±10.78	81.187 ±11.413	<0.001	157.09 ±19.09	90.304 ±7.477	<0.001	149.75 ±19.73	86.56 ±10.31	<0.001

Table 2: The correlation between insulin with (CRP and IL-6) for studied groups.

parameters	Female Patients NO.=16	Male Patients NO.=34	Total Patients NO.=50
IL-6 Pg/ml	0.392	0.472	0.435
CRP mg/l	0.393	0.482	0.467

DISCUSSION:

As shown in table (1) there was significant increase in insulin and pro-inflammation marker IL-6 and CRP in patients with acute myocardial infarction patients. It has been reported that measurement of inflammatory markers such as high-sensitivity C-reactive protein (HSCRP) is an important method for identifying individuals at risk for cardiovascular events [12] Yudkin et al. [13] reported that low but relatively elevated CRP in healthy subjects is related to insulin resistance when assessed by BMI, blood pressure, HDL-cholesterol, and triglyceride, and that increased proinflammatory cytokines, interleukin-6 and tumor necrosis factor-α (TNF-α), play an important role in the low level of chronic inflammatory state. [14]
Table (2) show positive correlation between insulin and CRP, Festa et al. [16] also reported that the level of CRP correlated with, insulin sensitivity (assessed by i.v. glucose tolerance test), and fasting plasma levels of insulin and proinsulin. They suggested that CRP is not only a predictor of cardiovascular events but also an independent predictor of insulin sensitivity. Several mechanisms
could explain the elevated level of CRP in acute myocardial infarction patients. First, CRP acts on vascular smooth muscle cells by up regulating the angiotensin type I receptor [17]
and stimulating the migration and proliferation of smooth muscle cells, in addition to the production of reactive oxygen species Inhibition of rennin–angiotensin system (RAS) by angiotensin receptor blocker (ARB) or ACE inhibitor (ACEI) results in a reduction of vascular smooth muscle cell proliferation,

stimulates NADPH oxidase and enhances production of reactive oxygen species (ROS), which in turn contributes to endothelial dysfunction by inactivating nitric oxide (NO). [14] Secondly, CRP has a direct effect on the endothelial cells and induces the secretion of specific chemokines, particularly monocyte chemoattractant protein-1, adhesion molecules, and E-selectin, whereas it decreases the expression of NO synthase. Furthermore, previous study demonstrated that several chemokines accelerated atherosclerosis, while the inhibition of chemokines reduced the atherosclerosis. In addition, activation or inhibition of NO differentially regulates atherosclerosis [14]

Furthermore, Steinberg et al. [17] reported that insulin-resistant states such as diabetes and obesity are associated with decreased endothelium-dependent vasodilation , and arterial compliance may be a partially NO-dependent process. In addition, insulin has been shown to induce vascular smooth muscle proliferation and migration in cell cultures. [14]

Animal studies have also suggested that, after balloon endothelial injury, hyperinsulinemia induces an increase in neointimal hyperplasia that was not seen in rats with streptozotocin-induced diabetes without hyperinsulinemia [14]. Finally, although our results document an association between insulin resistance and plasma CRP concentrations, they do not provide insight into the nature of this relation. For example, it has been suggested that heightened inflammatory responses could lead to insulin resistance and compensatory hyperinsulinemia. This has been attributed in large part to the important role of inflammatory cytokines released from adipocytes[18]. A process presumably made more likely with increased adiposity. Alternatively, metabolic abnormalities associated with insulin resistance, including hyperglycemia, elevated free fatty acids, dyslipidemia, and endothelial dysfunction, may induce cell activation and inflammatory responses. Moreover, insulin-resistant subjects appear to demonstrate an excess risk for the development of atherosclerosis, a condition that is in large part an inflammatory process. Therefore, insulin resistance could contribute to higher CRP concentrations. [19]

It has been proposed that long-term activation of the innate immune system may be involved in the development of insulin resistance and type 2 diabetes. One possible explanation for elevated inflammatory markers in obesity is that adipose tissue secretes a number of proinflammatory cytokines, including tumor necrosis factor-a (TNF-a) and interleukin-6 (IL-6) . Although immune cells, fibroblasts, endothelial cells, and monocytes have traditionally been regarded as the major sources of circulating IL-6, a recent study in which adipose tissue veins were selectively catheterized has indicated that a considerable proportion of circulating IL-6 is derived from

adipose tissue. The results also show positive correlation between insulin and IL-6. Circulating IL-6 levels have been reported to be elevated in obese people [20] The mechanisms by which IL-6 may modulate insulin secretion are not clear, although some evidence suggest that it may increase insulin secretion and preproinsulin mRNA expression via a $Ca2+$-dependent mechanism [11]. IL-6 may contribute to insulin resistance indirectly by stimulating lipolysis in adipocytes, thus resulting in an increase in circulating FFAs, which would impair insulin action [21]

CONCLUSION:

• The significant increase in insulin in AMI may be related to inflammation.

• Insulin positively correlated with inflammatory markers (CRP and IL-6).

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