The Impact of Inflammation on Adiponectin, IL-6 and CRP in Acute Myocardial Infarction Patients

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ABSTRACT:

BACKGROUND:

Adipose tissue is increasingly recognized as a key regulator of energy balance, playing an active role in lipid storage and buffering, and synthesizing and secreting a wide range of endocrine products that may be directly involved in the pathogenesis of the complications associated with obesity. Adiponectin is adipocyte derivate hormone that has important effect as anti-inflammatory factor. Inflammation contributes across the spectrum of cardiovascular disease, including the earliest steps in atherogenesis. IL-6 is one of the most important mediators of fever and of the acute phase response. C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation (an acute-phase protein). Myocardial Infarction (MI) or Acute Myocardial Infarction (AMI), is the interruption of blood supply to part of the heart, causing some heart cells to die.

OBJECTIVE:

To investigate the level of adiponectin and its effect on IL-6 and CRP in patients with Acute Myocardial infarction.

SUBJECTS AND METHODS:

The study included 50 patients with Acute Myocardial infarction and forty healthy subjects as control group. Levels of adiponectin , CRP and IL-6 were measured.

RESULTS:

The levels of adiponectin, IL-6 and CRP were significantly elevated with ($p<0.001$), there was negative correlation between adiponectin with CRP and IL-6 in acute myocardial infarction patients.

CONCLUSION:

The significant increase in adiponectin in AMI may be related to inflammation. Adiponectin inversely correlated with inflammatory marker (CRP and IL-6) so it has anti-inflammatory properties and that make us consider it as cardiovascular protective factor.

KEY WORD: adiponectin , crp, acute myocardial infarction.

INTRODUCTION:

Inflammation contributes across the spectrum of cardiovascular disease, including the earliest steps in atherogenesis. This recognition has had a profound impact on understanding the atherothrombosis as more than a disease of lipid accumulation, but rather as a disorder characterized by low-grade vascular inflammation. This concept can be used to predict future cardiovascular risk.[(1)]

Inflammatory responses are involved in the initiation and progression of atherosclerotic plaques. The majority of inflammatory cells infiltrating the arterial wall in early atherogenesis are monocytes. It has been suggested that the adipose tissue may play an important role in mediating this chronic inflammatory process and, subsequently, cardiovascular disease risk and therefore may not only be considered as a storage site for fat. [(2)]

IL-6 is one of the most important mediators of fever and of the acute phase response. In the muscle and fatty tissue IL-6 stimulates energy mobilization which leads to increased body temperature. IL-6 can be secreted by macrophages in response to specific microbial molecules, referred to as Pathogen Associated Molecular Patterns (PAMPs). These PAMPs bind to highly important group of detection molecules of the innate immune system, called Pattern Recognition Receptors (PRRs), including Toll-Like Receptors (TLRs). These TLRs are present on the cell surface and intracellular compartments

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and induce intracellular signaling cascades that give rise to inflammatory cytokine production. IL-6 is also essential for hybridoma growth and is found in many supplemental cloning media such as briclone. IL-6 is also produced by adipocytes and is thought to be a reason why obese individuals have higher
endogeneous levels of CRP(3). In a 2009 study, intranasally administered IL-6 was shown to improve sleep-associated consolidation of emotional memories. [3]

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation (an acute-phase protein). Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system. CRP is synthesized by the liver. [4] Myocardial Infarction (MI) or Acute Myocardial Infarction (AMI), commonly known as a heart attack, is the interruption of blood supply to part of the heart, causing some heart cells to die. This is most commonly due to occlusion (blockage) of a coronary artery following the rupture of a vulnerable atherosclerotic plaque, which is an unstable collection of lipids (fatty acids) and white blood cells (especially macrophages) in the wall of an artery. The resulting ischemia (restriction in blood supply) and oxygen shortage, if left untreated for a sufficient period of time, can cause damage or death (infarction) of heart muscle tissue. [5]

Adipose tissue is increasingly recognized as a key regulator of energy balance, playing an active role in lipid storage and buffering, and synthesizing and secreting a wide range of endocrine products that may be directly involved in the pathogenesis of the complications associated with obesity. So obesity is considered a major independent risk factor for atherosclerotic cardiovascular disease.

Adiponectin was first characterized in mice as a transcript over expressed in pre-adipocytes (precursors of fat cells) differentiating into adipocytes. The human homologue was identified as the most abundant transcript in adipose tissue. Contrary to expectations, despite being produced in adipose tissue, adiponectin was found to be decreased in obesity. This down regulation has not been fully explained. Supplementation by differing forms of adiponectin were able to improve insulin control, blood glucose and triglyceride levels in mouse models. The gene was investigated for variants that predispose to type 2 diabetes. [6]

SUBJECTS:

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

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 adiponectin, 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 exclude kidney diseases. Adiponectin, 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 was 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 CRP and adiponectin were compared between the study groups as in table (1). The patients with AMI were found to have significantly higher serum of IL-6 and CRP and adiponectin with($p<0.001$)

Table 1: The comparison between groups for (adiponectin,IL-6 and CRP) in studied groups.

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
Adiponectin g/ml	59.46 ±18.09	13.769±5 .095	<0.001	50.01 ±10.93	13.279 ±6.817	<0.001	54.68 ±13.88	13.48 ±2.09	<0.001
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

Relation between adiponectin with CRP

The results showed that there was strong negative correlation between adiponectin and CRP in female patient group (r=-0. 537) and between adiponectin and IL-6 in female patients group (r=-0.730)

The negative correlation was found between adiponectin and CRP in female control group (r=-0.360), in male patient group (r=-0.491), in total patient (r=-0.406) and in total control (r=-0.375) and between adiponectin with IL-6 in male patient group (r=-0.470), in male control group (r=-0.360), in total patient group (r=-0.414) and in total control (r=-0.350).

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

parameters	Female Patients NO.=16	Female Control NO.=16	Male Patients NO.=34	Male Control NO.=24	Total Patients NO.=50	Total Control NO.=40
IL-6 Pg/ml	-0. 730	-0.207	-0.470	-0.360	-0. 414	-0.350
CRP mg/l	-0.537	-0.360	-0. 491	-0. 309	-0.406	-0.375

DISCUSSION:

As shown in table (1) there was a significantly higher level of adiponectin in patients with AMI. Animal data support adiponectin as a cardiovascular protective molecule. In a mouse model of acute MI, adiponectin null mice responded with larger infarct sizes, greater myocardial cell apoptosis, and increased tumour necrosis factor expression when compared with wild-type controls. Rescue attempts with adiponectin delivered by adenovirus and recombinant adiponectin infusion prior to or during the ischaemia-reperfusion procedure, ameliorated all the associated damaging effects, suggesting that exogenous adiponectin protects the heart against ischaemic insults[8] That agree with our notice that the patients with higher levels of adiponectin have good prognosis.

Adiponectin was also demonstrated to inhibit

strongly the expression of adhesion molecules, including intracellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin Adiponectin was also shown to inhibit TNF-α-induced nuclear factor-κB activation through the inhibition of κB phosphorylation .

Suppression of nuclear factor-κB by adiponectin might be a major molecular mechanism for the inhibition of monocyte adhesion to endothelial cells (VCAM-1 play a pivotal role in the development of atherosclerosis. The expression of VCAM-1 is localized over the surface of endothelial cells in lesion-prone sites). Adiponectin also inhibits the expression of the scavenger receptor class A-1 of macrophages,

resulting in markedly decreased uptake of oxidized low-density lipoprotein by macrophages and inhibition of foam cell formation. In addition, in cultured smooth muscle cells, adiponectin attenuated DNA synthesis induced by growth factors including platelet-derived growth factor, heparin-binding epidermal growth factor (EGF)-like growth factor, basic fibroblast growth factor, and EGF, as well as cell proliferation and migration induced by heparin binding EGF-like growth factor. [9]

Atul Singhal [11] studied adiponectin in vitro and suggested that adiponectin reduces the development of atherosclerosis by stimulating the production of nitric oxide from vascular endothelial cells. [11]

On the other hand, low adiponectin levels are associated with reduced expression of nitric oxide, and increased expression of angiotensin II and cellular adhesion molecules from the endothelium. [10]

In humans, there are many offensive factors, including oxidized LDL, inflammatory stimuli, and chemical substances that may induce vascular injuries. At that time, adiponectin secreted from adipose tissues may go into the injured arteries and protect against the development of atherogenic vascular changes. Therefore, adiponectin might be likened firefighters who put out the fire of the vascular walls while it is still small. When the plasma levels of adiponectin are decreased in the subjects with visceral fat accumulation, the small fire may become bigger and bigger because of the shortage of firefighters[12].

The mortality rate was also inversely related to BMI, most probably reflecting the known association of cardiac 'wasting' with increased mortality, suggesting that the paradoxical increase of adiponectin levels in those with the highest mortality may have been secondary to weight loss, a known stimulator of adiponectin.

Despite all the counter-regulatory mechanisms that are mobilized in the high-risk patients, including up-regulation of plasma adiponectin levels, it is intuitive that the reparative processes of the body may be overwhelmed, translating into higher cardiovascular morbidity. The anti-inflammatory effects of adiponectin indicate that it is an interesting protective factor for atherosclerosis development, particularly in those clinical situations associated with low plasma concentrations of adiponectin. It is conceivable that the use of recombinant adiponectin may become beneficial in the prevention of cardiovascular disease in selected patients. That suggest the increasing plasma adiponectin might be useful in preventing vascular restenosis after vascular intervention[13].

Further investigations in patients with the above-mentioned states and other hypoadiponectinemic conditions are required to clarify these aspects of the potential therapeutic applications of this adipocytokine.[14]

Osamu et al 2009 [15]demonstrated a novel effect of natriuretic peptides (ANP and BNP) on the production of adiponectin by adipocytes in both experimental and clinical studies. By:

-First, they clearly demonstrated that pathophysiological and pharmacological concentrations of either ANP or BNP increased adiponectin synthesis by primary cultured human adipocytes.

-Second, they showed that administration of recombinant ANP increased the plasma adiponectin level. This study showed negative correlation between adiponectin with CRP in table (2). While this observation may be explained by the co llinearity between CRP and IL-6, it is pertinent that both adiponectin and IL-6 are adipocyte derived products and their concordance could represent a co-secretory response after accounting for the variability in IL-6 levels that is represented by CRP. [16]

As shown in table (1) it was found that CRP significantly higher in patients group than control groups, study by (Kawabe, H and Saito,2010) [16] has clearly shown that elevated plasma C-reactive protein (CRP) was associated with the future development of hypertension in dose-dependent manner. These finding suggest that hypertension may be an inflammatory disease that is associated with obesity and the metabolic syndrome. This could represent a causative pathway by which inflammation predisposes to both arterial stiffness and hypertension as well as to cardiovascular and renal disease. [16] CRP binds to a large number of autologous and extrinsic ligands, including native and modified plasma lipoproteins, phospholipids, and apoptotic cells, which are present in the atherosclerotic lesions. When bound to ligands, CRP activates the classic pathway of complement, a major player in the immune and inflammatory response, and reacts with Fcγ receptors on phagocytic cells. Both CRP and complement are known to colocalize in human atherosclerotic lesions, which suggests that CRP, by activating the complement, may be

an active participant in atherosclerosis development. [17]

In vitro experiments showed that CRP modulates the activity and expression of multiple factors implicated in atherogenesis. It down regulates endothelial nitric oxide synthase (eNOS) and stimulates the production of endothelin-1 (ET-1) in endothelial cells in vitro. CRP may also facilitate leukocyte adhesion and internalization into the arterial wall by stimulating the expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1, E-selectin, and monocyte chemoattractant protein-1. Moreover, CRP itself was found to be chemotactic for monocytes; it also binds to oxidized LDL and facilitates the uptake of LDL by macrophages. [17]

CRP increases smooth muscle cell (SMC) migration and neointimal formation after carotid angioplasty in rats. It may also activate nuclear factor-κB and activator protein-1 (AP-1) and up regulate angiotensin type 1 receptors (AT1-R) in human vascular SMCs, which could mediate many of the proinflammatory effects of angiotensin (Ang) II. (Ang II has been reported previously to be associated with increased expression of both VCAM-1 and collagen in animal models. [17], this is the mechanism of CRP in developing atherosclerosis that explain the relation of elevated level of CRP as in table (1) in patients with AMI.

CRP can also have an effect on plasminogen activator –inhibitor-1 (PAI-1 that is a key regulator of fibrinolysis by inhibiting tissue plasminogen activator (tPA). It has been proposed that increased PAI-1 in the vessel wall can promote formation of plaques with lipid-laden cores and thin fibrous caps, which are more prone to rupture. Study by Sridevi et al in 2008[18] showed that CRP augments the stability of PAI-1 mRNA. Previously, insulin and cytokines have been shown to augment PAI-1 release via increasing mRNA stability CRP has been shown to augment endothelin-1 (ET-1) and interleukin 6 (IL-6) and thereby contribute to increased ICAM-1, VCAM-1, and MCP-1 in human saphenous vein endothelial cells.[18]

A critical enzyme present in endothelial cells is endothelial nitric oxide synthase (eNOS). Nitric oxide derived from eNOS promotes arterial vasodilatation and inhibits smooth muscle cell proliferation, LDL oxidation, platelet adhesion and aggregation, and monocyte adhesion to endothelium. It is believed that endothelial dysfunction (decreased eNOS bioactivity) occurs very early in atherogenesis. CRP causes a decrease in eNOS expression and bioactivity, especially at the higher concentration.[19]

The fact that foam cells in early lesions stain positively for the CRP-R as well as CRP is consistent with the hypothesis that CRP participates in foam cell formation by opsonizing lipid particles. Co localization of CRP with so-called enzymatically degraded LDL (E-LDL) was demonstrated in early atherosclerotic lesions.[19]

Although there is evidence that foam cell formation by E-LDL is in part due to lipoprotein uptake via a scavenger receptor–mediated pathway, cellular uptake of E-LDL may be accompanied by the uptake of bound CRP and mediated by the CRP-R. CRP is internalized by macrophages via the endosomal route and is partially degraded, followed by recycling of the CRP-R. CRP may be an important component of the plasma proteins insulating the arterial wall preceding the so-called initial atherosclerotic lesion, which is characterized by the first appearance of monocyte-derived macrophage foam cells. Monocyte infiltration into the arterial wall is a 2-step process that involves adherence to the activated endothelium first and directed migration to a chemotactic gradient second. Diffusely deposited CRP may generate a chemotactic gradient within the arterial wall, attracting monocytes that have transmigrated the endothelium. This finding can agree with our finding because our patients with elevated level of CRP have bad prognosis.

Nonetheless, early accumulation of native CRP in insudated areas may partly explain some of the phenomena in atherosclerotic lesion formation that are hitherto not understood. First, in addition to other chemoattractants, eg, monocyte chemotactic protein-1, CRP may act as a chemoattractant for blood monocytes in vivo. Second, CRP is known to inhibit neutrophil chemotaxis and the binding of neutrophils to endothelial cells. [20]

Further, C-reactive protein has been shown to exert direct adverse effects on the vascular endothelium by reducing nitric-oxide release and increasing endothelin-1 production, as well as by inducing expression of endothelial adhesion molecules.[20] Patients with persistently elevated IL-6 levels demonstrate a worse in-hospital outcome. Raised levels of IL-6 are often found correlated to CRP levels, consistent with IL-6 being the main stimulant for the hepatic

production of CRP. [20]In normal conditions, the heart does not express cytokines. However, during an ischemic event , they may be up to 50 times in the culprit ischemic region and up to 15 times in the adjacent (non ischemic) zones. In the early post (Myocardial Infarction) MI phase, a certain degree of cytokines production is physiological, because in this phase cytokines play an important cyto-protective role by reducing cell apoptosis. Usually, in the case of small MI, tissue cytokine levels rapidly return to zero. In larger MI, cytokines may persist at very high levels and further being long time detectable also in the normal adjacent myocardium. This phenomenon produces unfavorable myocardial remodeling finally worsening clinical outcomes. Cytokines also play pivotal roles in the pathogenesis of atherosclerosis. [21] That agree with our results in table (1) and contributed to explan the significantly higher level of IL-6 in AMI patients.

CONCLUSION:

- The significant increase in adiponectin in AMI may be related to inflammation.
- Adiponectin inversely correlated with inflammatory marker (IL-6 and CRP) so it has anti-inflammatory properties that make us consider it as cardiovascular protective.

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