Serum Levels of Adiponectin and Ghrelin in Patients with Acute Myocardial Infarction

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Abstract: Background: Inflammation is widely known to play a key role in the development and progression of cardiovascular diseases. It has been observed that adipokines play an increasingly large role in systemic and local inflammation. Therefore, adipose tissue may have a more important role than previously thought in the pathogenesis of several disease types. We study serum levels of adiponectin and ghrelin in patients with acute myocardial infarction (AMI) with study of some of cardiovascular risk factors. **Methods:** We analyzed 64 patients with acute myocardial infarction admitted at our emergency unit and 20 age and sex matched healthy controls. Clinical parameters, glycemic, lipid profile, tumor necrosis factor- α (TNF-α), interleukin -6 (IL-6), serum insulin, insulin resistance (HOMA-IR), as well as serum adiponectin and ghrelin were assayed. **Results:** We found significantly ($P < 0.01$) increased levels of TNF-α, IL-6, insulin, and HOMA-IR in patients with AMI rather than healthy controls. Plasma adiponectin levels and ghrelin were significantly decreased ($P < 0.01$) compared to those of controls. We found significant correlations between plasma adiponectin levels and BMI, hypertension, TNF-α and IL-6. In the case of ghrelin, we found significant correlations with BMI, HDL-C, diabetes mellitus and fasting glucose. **Conclusions:** Low serum adiponectin and ghrelin level may be risk factor for AMI independent of other traditional cardiovascular risk factors and may provide a novel therapeutic target.

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1. Introduction

Inflammation is widely known to play a key role in the development and progression of cardiovascular diseases. It is becoming increasingly evident that obesity is linked to many proinflammatory and obesity associated cardiovascular conditions. It has been observed that adipokines play an increasingly large role in systemic and local inflammation. Therefore, adipose tissue may have a more important role than previously thought in the pathogenesis of several disease types (Aprahamian and Sam, 2011). Recently, it has become apparent that adipose tissue is an active endocrine and paracrine organ that releases several bioactive mediators. Those substances influence body weight homeostasis, inflammation, insulin resistance, and diabetes, but their precise role in atherosclerosis has not been elucidated fully (Shah *et al*., 2008). Adiponectin and ghrelin have emerged as novel adipokines, adipose tissue-specific protein but their role in coronary artery disease remains obscure. The adiponectin monomer (30 kDa) has a structure consisting of a globular head and a collagenous tail, and this monomer is able to multimerize to form several stable complexes of low, medium, and high molecular weight. Adiponectin shares sequence homology with collagens VIII and X as well as complement factor C1q. It has previously been referred to as ACRP30 for adipose complement related peptide of 30 kDa based upon its homology to C1q (Scherer *et al*., 1995). Ghrelin, a stomach-derived hormone, functions in multiple biological processes including glucose metabolism, adipogenesis, cell differentiation, and proliferation (Cordido *et al*., 2009). *In vitro* data suggest a dual role of ghrelin proatherogenic in the early phase and antiatherogenic in the advance stage of coronary artery disease (Kellokoski *et al*., 2009).

2. Subjects and Methods:

Subjects and study design:

The study population included 64 (52 males and 12 females) subjects, aged 40 to 66 years, who consecutively were admitted at our emergency unit from June 2010 to July 2011. It was approved by the faculty committee for research ethics. Patients who participated in this study gave informed consent. Participants were assigned to 2 groups:

1- AMI (64) on admission. The AMI diagnosis was made on the basis of typical symptoms consistent with myocardial ischemia (chest discomfort), newly developed ischemic ST-T changes (ST-elevation or ST-segment depression or prominent T-wave inversion) in at least 2 contiguous ECG leads, and elevated cardiac associated biomarkers CK-MB and troponin I.

2- Healthy controls (20). Age and sex matched individuals, without any chronic metabolic or

cardiovascular disease or overt cardiac origin symptoms. None of the controls was receiving any long term medication or was suffering from an acute infection.

The exclusion criteria: was the history of AMI within the past 6 months, the significant concomitant diseases such as autoimmune disease, infection, malignancy, chronic heart failure, and severe chronic liver or renal disease.

Methods:

Venous blood samples were collected on admission and following an overnight fasting, lipogram parameters, fasting serum glucose, liver function testes and renal function testes were analyzed on autoanalyzer Cobas c 311 (Roche/Hitachi cobas c systems). We quantified CK-MB, troponin-I and serum insulin using the two-site immunoenzymometric assay method (TOSOH, AIA 600II). The glycosylated hemoglobin (HbA_{1c}) was determined by high performance liquid chromatography (The BioRad D10 analyser). Body mass index (BMI, kg/m^2) was assessed. The insulin resistance was estimated by a homeostasis model assessment (HOMA-IR) index with the following formula: HOMA-IR = fasting insulin (μIU/ml) x fasting glucose (mg/dl)/405. Measurement of IL-6 was performed by kits from biosource Europe. Measurement of TNF-α was performed using Quantikine, R&D Systems, Inc. Serum concentrations of adiponectin performed using Quantikine R&D Systems; Inc. These assays employ the quantitative sandwich enzyme immunoassay technique. Serum levels of ghrelin were assayed using competitive enzyme immunoassay kits (DRG International Inc., USA, 3706).

Statistical analysis:

The data are presented as mean ± standard deviation (SD) and number (n). Linear relationships between variables were determined using Pearson's correlation coefficient. The differences between groups were compared by T-test and ANOVA test. Statistical significance is considered a value of $P < 0.05$. All statistical analyses were performed using SPSS software, version 10.0.

3. Results:

Table 1, show age, sex and frequencies of each risk factor of study group. The subjects consisted of 52 men and 12 women with a mean age of 55±11 years. Thirty-seven subjects had hypertension and dyslipidemia was present in 35 subjects. Cigarette smoker was present in 49 subjects and 23 diabetic one. Table 2, depicts clinical characteristics and laboratory variables. We found significantly ($P < 0.01$) increased levels of TNF-α, IL-6, insulin, and HOMA-IR in patients with AMI rather than healthy controls. AMI groups had inadequate glycemic control. Plasma adiponectin levels were significantly decreased ($P < 0.01$) compared to those of controls. Serum ghrelin levels significantly decreased across the patients group, compared with the healthy controls group ($P < 0.01$). Diabetic patients with AMI had significantly ($P < 0.05$) downregulated ghrelin levels than the nondiabetic patients. In the case of ghrelin, we found significant correlations with BMI, HDL-C, diabetes presence and fasting glucose. We found significant correlations between plasma adiponectin levels and BMI and hypertension (Table 3). In our study there is no significant correlation between adiponectin or ghrelin level and CK-MB or troponin-I but we found significant correlations between plasma adiponectin levels and TNF-α and IL-6 (Table 4).

Table I: Age, sex and frequencies of each risk factor of study group

Age (range)	40–66 years
Male : Female	52:12
Dyslipidemia (%)	54.7%
Diabetic : Non-Diabetic	23(35.9%): 41(64.1%)
Hypertensive : Non-Hypertensive	37(57.8%): 27(42.2%)
Smoker : Non-Smoker	49(76.6%): 15(23.4%)

Table 2: Clinical and laboratory variables of studied groups

	AMI (n=64)	Controls (n=20)	*p*-value
BMI (kg/m^2)	24.3±0.41	20.3±0.21	> 0.05
CK-MB (ng/ml)	20±5.3	1.5±0.42	< 0.01
Troponin –I (ng/ml)	2.3±0.5	0.01±0.06	< 0.01
Chol (mg/dl)	197±5.4	107±9.4	< 0.05
HDL-C (mg/dl)	48±2.7	45±3.8	> 0.05
LDL-C (mg/dl)	122.5±54.2	112.5±44.2	> 0.05
TG (mg/dl)	164±8.1	104±3.1	< 0.05
F. glucose (mg/dl)	153.5±73	85.2±23	< 0.05
HbA_{1c} (%)	7.2±1.9	5.2±0.9	< 0.05
Insulin (μIU/ml)	25±2.2	15±2.6	< 0.01

HOMA-IR	9.4±4.38	3.15±3.3	< 0.01
Adiponectin (µg/ml)	3.2±1.9	8.1±3.5	< 0.01
Ghrelin (ng/ml)	10.2±0.9	43.6±2.3	< 0.01
TNF-α (pg/ml)	39±9.8	12±2.1	< 0.01
IL-6 (pg/ml)	59±35	7±1.2	< 0.01

CK-MB, Creatine Kinase MB; Chol, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HbA_{1c}, hemoglobin A_{1c}; F.glucose, fasting glucose

Table 3: Correlation between serum adiponectin, ghrelin & other cardiovascular risk factors

	Adiponectin		Ghrelin	
	r	*p* -value	r	*p* -value
BMI	-0.360	0.02*	-0.299	0.04*
Smoking	-0.315	0.36	-0.362	0.62
Hypertention	-0.315	0.04*	-0.192	0.33
DM	-0.172	0.42	-0.245	0.04*
Chol	-0.175	0.54	-0.165	0.06
HDL-C	0.182	0.22	0.312	0.01*
LDL-C	-0.123	0.25	-0.421	0.05
TG	-0.192	0.22	-0.325	0.12
F.glucose	-0.072	0.52	-0.315	0.02*

DM, diabetes mellitus * significant: $p < 0.05$

Table 4: Correlation between serum adiponectin, ghrelin & CK-MB, troponin-I and pro- inflammatory cytokines

	Adiponectin		Ghrelin	
	r	*p* -value	r	*p* -value
CK-MB	-0.360	0.42	-0.299	0.44
Troponin-I	-0.315	0.36	-0.362	0.62
TNF-α	-0.386	0.04*	-0.192	0.33
IL-6	-0.423	0.02*	-0.245	0.64

* Significant: $p < 0.05$

4. Discussion:

The present study demonstrated significantly lower adiponectin and ghrelin serum levels in patients with acute myocardial infarction compared with healthy individuals. The most pronounced elevation of inflammatory markers, TNF-α and IL-6 levels were documented in the AMI patients group with significant negative correlations between them and adiponectin serum levels. Low plasma adiponectin has been associated with myocardial infarction in young patients independent of other conventional risk factors (Persson *et al*., 2010). Adiponectin inhibits the expression of TNF-*α* in adipocytes, and both TNF-*α* and IL-6 inhibits the production of adiponectin (Fasshauer *et al*., 2003; Maeda, *et al*., 2001)), these data suggest that the metabolic consequences observed in obesity may be related to an imbalance of pro- and anti-inflammatory cytokines. Thus, adipokines contribute to the pathophysiology of obesity linked disorders through their ability to modify proinflammatory and metabolic processes. Adiponectin also exerts anti-hypertrophic effects and protects against ischemia-reperfusion injury (Shibata *et al*., 2007; Shibata *et al*., 2004), and it mediates protective effects in obesity related metabolic and vascular disease presumably by its anti-inflammatory actions and protects the heart against ischemia reperfusion injury through its ability to suppress myocardial inflammation and apoptosis (Shibata *et al*., 2005). Adiponectin has anti-atherosclerotic, as well as anti-inflammatory properties that may play an important role in preventing the progression of coronary artery disease. Results from clinical surveys show that low adiponectin levels, while being a predictive marker for early stage atherosclerosis, are also significantly associated with coronary artery disease (Kumada *et al*., 2003). In healthy individuals, adiponectin maintains anti-inflammatory properties, but in Disease states where adiponectin levels decrease result in proinflammatory signaling and exacerbation of disease (Aprahamian and Sam, 2011). Ghrelin, has been implicated in diabetes and insulin sensitivity (Kadoglou *et al*., 2010b), but its precise role in atherosclerosis development has not been clarified fully yet (Kadoglou *et al*., 2008; Skilton and Celermajer, 2006). This study is in consistent with another study which demonstrating low ghrelin

serum levels in patients with AMI compared with the control group independent of other cardiovascular risk factors (Kadoglou et al., 2010a). Thus, our results indicate a role of ghrelin in coronary atherosclerosis development. Otherwise, there are controversial clinical data about the involvement of ghrelin in carotid atherosclerosis. Future studies will elucidate the protective role of ghrelin in atherosclerosis progression. The role of ghrelin in atherosclerosis seems quite complex, and basic research studies have documented either proinflammatory or anti-inflammatory properties (Yano *et al*., 2009).

Conclusion:

Our study suggests that the low serum adiponectin and ghrelin level may be risk factor for AMI independent of other traditional cardiovascular risk factors. They may be two promising, clinically important proteins, which link adiposity, inflammation, and atherosclerosis and provide a novel therapeutic target.

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