Association of Admission Serum Resistin Level with Acute ST-Segment Elevation Myocardial Infarction in Iraqi Patients

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Abstract

Human resistin is an adipokine, with a possible link to coronary heart disease.A few studies were done about resistin in acute phase of ST-segment elevation myocardial infarction (STEMI) especially in Iraqi patients. Accordingly we design a study to investigate the association between resistin concentration and acute phase of STEMI in Iraqi patients.

The present study was carried out at Al-Yarmouk Teaching Hospital from December 2011 until June 2012. Serum resistin levels were measured in 50 patients with acute STEMI (mean age: 58.16 ± 11.73 years) at the first 12 hours of admission and 34 normal controls (mean age: 53.98 ± 15.46 years) matched for age, sex and other risk factors.

Resistin level in patients with acute STEMI (13.08 ng/mL) was significantly higher than that of the control group (5.31 ng/mL) ($p < 0.0001$). The study revealed a significant negative correlation between serum resistin level and serum adiponectin level among patients.

Key words: Resistin, acute ST-segment elevation myocardial infarction, adipokines.

العلاقة بين مستوى الرسستين في مصل الدم مع احتشاء عضلة القلب الحاد

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الخلاصة

هرمون الرسستين هو احد الاديبوكاينات مع علاقة محتملة بأمراض القلب التاجية. هنالك القليل من ال دراسات التي عُمِلتْ عن الرسستين في المرحلة الحادّةِ مِنْ احتشاء عضلة القلب خصوصاً في المرضى العراقيين. طبقا لذلك تم تصميم هذه الدراسة لتَحرّي العلاقة بين تركيزِ الرسستين واحتشاء عضلة القلب الحاد في المرضى العراقيين.

الدراسة الحالية نُفّذتْ في مستشفى اليرموك التعليمي مِنْ كانون الأولِ 2011 حتى حزيرانِ 2012. تم قياس مستوى هرمون الرسستين في مصل الدم لدى 50 مريضا من مرضى احتشاء عضلة القلب الحاد (معدل العمر 58.16± 11.73 سنة) في الساعات الـ 12 الاولى من دخولهم المستشفى بالاضافة الى قياسه لدى 34 شخصا اخر (معدل العمر 53.98± 15.46 سنة) كمجموعة ضابطة متوافقة مع مجموعة المرضى من ناحية العمر والجنس وعوامل خطرِ أخرى.

كشفت الدراسة ان مستوى هرمون الرسستين في مصل الدم لدى مرضى احتشاء عضلة القلب الحاد والبالغ (13,8 نانوغرام / مل)كان أعلى جداً مِنْ مستواه في المجموعة الضابطة والبالغ (5,31 نانوغرام/ مل) .

كما ان الدراسة قد كَشفتْ عن وجود إرتباط سلبي هامّ بين مستوى هرمون الرسستين في مصل الدم ومستوى هرمون الأديبونيكتين بين المرضى.

الكلمات المفتاحية :رسستين ، احتشاء عضلة القلب الحاد ، اديبوكاينات .

Introduction

Complications of atherosclerosis remain the primary cause of death in most countries despite massive efforts to limit well-documented risk factors such as smoking, hypertension, hyperlipidemia, diabetes mellitus, and obesity. The relationship between obesity and atherogenesis is multifactor, including changes in blood pressure (BP), alterations in the composition and plasma level of lipoproteins, coagulation and inflammatory factors [(1)].

Recent advances in the knowledge of adipose tissue give evidence that it is a secretary organ, producing a variety of adipokines that may be relevant for development or progression of atherosclerotic vascular disease [(2)]. Resistin, the product of the RSTN gene, was discovered in 2001 by the group of Mitchell Lazar as a target gene of the anti-diabetic drug thiozolidinedione (TZD), which was down-regulated in mouse adipocytes upon treatment [(3)].

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It was named resistin because of the acquired insulin resistance that mice injected with resistin demonstrated [3-5]. Resistin is a ~12.5 kDa peptide hormone that belongs to the Resistin Like Molecules (RELM) family (also known as Adipose Tissue Specific Secretory Factor, ADSF, or Found in Inflammatory Zone, FIZZ, family) of cystein-rich secreted proteins [6]. In rodents, resistin is derived almost exclusively from fat cells [3, 7, 8], whereas in humans resistin is produced by inflammatory cells, primarily macrophages [9].

The relationship between resistin and coronary artery disease (CAD) has been controversial [10]. In humans, monocytes and macrophages produce large quantities of resistin, but very little resistin is expressed in adipocytes [11]. Resistin has been suggested to be an inflammatory marker in humans, because macrophages are known inflammatory modulators. This suggests a possible link between resistin and cardiovascular (CV) disease via proinflammatory pathways [12].

Resistin was suggested to affect endothelial function and the migration of vascular smooth muscle cells [13-15], which are regarded as key pathophysiological mechanisms of atherosclerosis. Further, resistin has been noted to play a vital role in increasing the level of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) in an obese person which is directly atherogenic [16-18].

Although several studies have been done on resistin and CAD, but most of them have been conducted on patients with chronic ischemia and the studies in acute phase of ST-segment elevation myocardial infarction (STEMI) especially in developing countries are limited and rare. The present study was designed to evaluate the association between admission serum levels of resistin and acute STEMI in Iraqi patients as well as examining possible associations and correlations between resistin and selected demographic , clinical and laboratory variables among patients with STEMI.

Subjects and Method

Subjects

The present study was carried out at Al-Yarmouk Teaching Hospital from December 2011 until June 2012. The study protocol was approved by the scientific committee in the College of Pharmacy, University of Baghdad and the Medical Ethics Committee in the ministry of health / republic of Iraq. This case-control study was conducted on fifty (50) patients who were treated for acute STEMI with the following inclusion criteria:

1 .First experience of acute MI.

2 .Absence in the electrocardiogram (ECG) of conditions that might complicate the interpretation of the ST segment, such as bundle branch block, preexcitation, atrial fibrillation, atrial flutter, or complete atrioventricular block.

3 .A maximum of 12 hours between the onset of symptoms and initiation of thrombolytic therapy.

The diagnosis of acute MI was made on the basis of a history of chest pain lasting for more than 30 minutes that is associated with ECG changes suggestive of ST-segment elevation of 1mm or more in at least 2 contiguous leads and is unresponsive to nitroglycerin administration. The diagnosis was subsequently be confirmed by elevation of serum cardiac troponin I (cTnI) activity. All the patients involved in the study were followed up clinically during entire hospitalization period to assess them for response to thrombolytic therapy as well as for the development of any complications.

In addition thirty four (34) subjects were selected as a control group and matched them with case group for age, sex and other CAD risk factors such as hypertension, diabetes mellitus, hyperlipidemia, body mass index (BMI), smoking and renal function.

Laboratory analysis

Blood samples were collected from all patients by vein puncture (5ml), at admission before initiation of alteplase and 6-9 hours later to measure the studied parameters.

The sample was transferred into clean plain tube, left at room temperature for at least 30 minutes for clotting, centrifuged, then serum separated to be used for measuring the studied parameters. Serum resistin level was determined using enzyme linked immunosorbent assay (ELISA) (Demeditec® Diagnostics (Germany)) in patients and control groups.

In addition, ELISA kits were used to determine serum level of cTnI (Troponin I ELISA Kit, Oxis® International, Inc (USA)), leptin (Leptin ELISA Kit, RayBio® ELISA kits (USA)), and adiponectin (adiponectin ELISA Kit, Demeditec® Diagnostics (Germany)) in patients and control groups.

Statistical Analysis

Statistical analysis was performed by SPSS (version 11; SPSS, Inc., Chicago, IL).

Nominal variables are compared using chi-square test. Continuous variables were summarized as mean ± standard deviation (SD). Continuous variables are tested for normality

using Shapiro Wilk test. Normally distributed variables are compared using t-test. Non-normally distributed variables are compared using Mann- Whitney U test.

Spearman correlation was performed to evaluate the relationship between resistin level and the values of other selected clinical variables among patients with STEMI. In all cases, a probability value $P<0.05$ was considered statistically significant.

Results

Demographic, clinical characteristics and baseline laboratory variables of the study groups.

The demographic and clinical characteristics of the study groups, as well as laboratory variables are shown in table 1. No significant differences were observed between the patients and the control groups in all of these parameters.

Table 1: Demographic, clinical characteristics and baseline laboratory variables of the study groups.

	Patients	Control	P value
Number of patients	50	34	0.08 a
Males	41	25	0.74 a
Females	9	9	0.45 a
Age (yr)	58.16 ± 11.73	53.98 ± 15.46	0.16 b
BMI (kg/m^2)	28.05 ± 4.27	27.89 ± 3.50	0.96 c
Diabetes	15	4	0.11 a
Hypertension	18	12	0.96 a
Smoking	26	8	0.08 a
S. Uric acid (mg/dl)	4.94± 1.32	5.12± 1.24	0.37 c
S. Creatinine (mg/dl)	0.91 ± 0.31	0.85 ± 0.28	0.37 c
S. Urea (mg/dl)	39.12 ± 11.16	37.20± 8.06	0.67 c
S. Total cholesterol (mg/dl)	199.62± 41.09	189.26± 28.35	0.09 c
HDL-c (mg/dl)	41.03± 4.79	43.17± 10.56	0.36 c

BMI: body mass index, **HDL-c**: high density lipoprotein cholesterol. **a**: chi-square test, **b**: t.test, **c**: Mann-Whitney U test.

Resistin level in the patients and control groups

Results presented in table 2 showed that serum resistin level in patients with STEMI on admission was significantly higher than those in the control group (13.08 ± 2.53 ng/ml vs. 5.31 ± 0.87 ng/ml, $p < 0.0001$).

Table 2: Admission serum resistin level in STEMI patients compared to control.

	Patients (n=50)	Control (n=34)	P value
Serum resistin (ng/ml)	13.08 ± 2.53	5.31 ± 0.87	p < 0.0001

Values are presented as mean ± SD; n=number of patients.

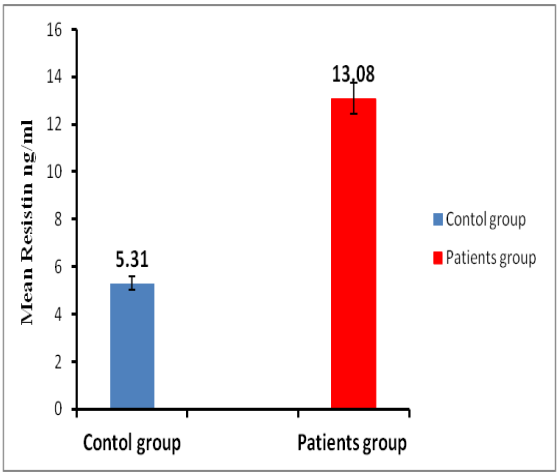

Figure 1: Admission serum resistin level in STEMI patients compared to control.

Association of admission resistin level with selected clinical variables among patients with STEMI

Studying the association between admission serum resistin level and selected clinical variables among patients with STEMI (diabetes, hypertension, sex, location of MI, development of heart failure (HF), development of atrial fibrillation (AF), development of ventricular tachycardia (VT) and/or ventricular fibrillation (VF), and achievement of successful reperfusion) revealed a highly significant difference in serum resistin levels between male and female patients ($p < 0.001$). No significant differences were present for the remaining variables as shown in table 3.

Table 3: Association of admission resistin level to selected clinical variables among patients with STEM.

		Resistin level (ng/ml)		P value
		Yes	No	
1	Diabetes	12.70 ± 3.01 (n=15)	13.24 ± 2.33 (n=35)	0.49 a
2	Hypertension	13.76 ± 2.71 (n=18)	12.69 ± 2.34 (n=32)	0.14 a
3	Male gender	12.38 ± 2.23 (n=41)	16.24± 0.89 (n= 9)	< 0.001** b
4	Anterior MI	13.15 ± 2.50 (n=31)	12.95 ± 2.65 (n= 19)	0.77 b
5	Development of HF	12.4 ± 2.77 (n=9)	13.23 ± 2.49 (n=41)	0.38 b
6	Development of AF	13.71 ± 3.37 (n=6)	12.86 ± 2.44 (n=44)	0.38 b
7	Development of VT and/or VF	13.64 ± 2.68 (n=5)	12.89 ± 2.54 (n=45)	0.49 b
8	Successful reperfusion	13.90 ± 2.83 (n=12)	12.82 ± 2.42 (n=38)	0.14 b

Values are presented as mean ± SD; **n**=number of patients. **Hf** : heart failure, **AF**: atrial fibrillation, **VF**: ventricular fibrillation, **VT**: ventricular tachycardia. **a**: t.test, **b**: Mann-Whitney U test. ** Highly significant ($p < 0.001$).

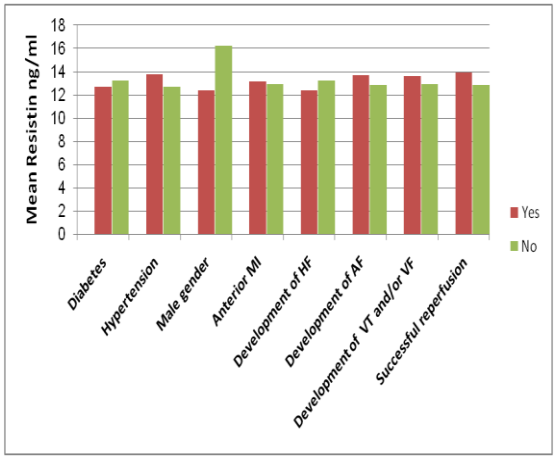

Figure 2: Association of admission resistin level to selected clinical variables among patients with STEMI.

Correlation between serum resistin and selected demographic and laboratory variables in STEMI patients

Studying the correlation between admission serum resistin level and selected demographic and laboratory variables among patients with STEMI (Age, BMI, S. uric acid, S. Creatinine, S. urea, S. Total cholesterol, HDL-c, serum leptin, serum adiponectin and serum cTnI) revealed a significant negative correlation between plasma resistin level and adiponectin level. No significant correlation was found between age, BMI, S. uric acid, S. Creatinine, S. urea, Total cholesterol, HDL-c, serum leptin, and serum cTnI and resistin level (Table 4).

Table 4: Correlation between serum resistin level and selected demographic and laboratory variables in STEMI patients.

		Correlation coefficient	P value
1	Age	0.236	0.099
2	BMI	0.080	0.580
3	S. Uric acid	0.045	0.757
4	S. Creatinine	-0.040	0.781
5	S. Urea	0.195	0.175
6	S. Total cholesterol	0.027	0.851
7	S. HDL-c	-0.065	0.651
8	Serum leptin	0.058	0.688
9	Serum adiponectin	-0.861	<0.0001**
10	Serum cTnI	0.232	0.105

BMI: body mass index, **S. HDL-c**: serum high density lipoprotein cholesterol.

Discussion

In this case-control study, we found that the serum resistin values were significantly increased in patients with acute STEMI, when compared with controls. These results are in agreement with similar studies done in patients with acute myocardial infarction [19- 21].

However, there are still controversies about the association of resistin with CAD. Burnett *et al* showed that resistin was not independently associated with CAD [22]. Anyhow, it was reported that resistin levels are substantially higher in human inflammatory cells when compared with human adipocytes (Patel *et al*., 2003;Yang *et al*., 2003; Kaser *et al*., 2003)[9, 11, 23]. Elevation of resistin in the acute coronary syndrome (ACS) might represent the presence of inflammatory process in mononuclear cells-precede myocardial necrosis. These findings may additionally support the hypothesis that in the conditions of the ACS resistin might represent inflammatory rather than a metabolic processes [24].

It has been suggested that resistin may mediate partly its pro-atherosclerotic properties by influencing systemic inflammation [11] .Patients with acute coronary syndrome had coronary plaques with more extensive macrophage-rich areas, which was the major source of resistin [23]. Inflammatory responses stimulated resistin secretion, and resistin could also promote production of pro-inflammatory mediators such as interleukin-6 (IL-6) partially by activation of nuclear factor-κB signaling pathway, hence aggravate the pro- inflammatory response by a positive feedback [25]. Moreover, resistin could affect the functions of vascular cells and exerts direct effects to promote endothelial cells activation by promoting endothelin-1 (ET-1) release [26].

Resistin has been shown to impair endothelium-dependent dilation of coronary vessels induced by the cardioprotectant bradykinin (Dick *et al*., 2006) [27]. Lubos *et al*. (2007) proposed resistin as a diagnostic marker of MI and future cardiovascular death [21]. Despite the fact that resistin exhibits properties commonly associated with cardioprotective agents, based on evidence obtained in animal models of obesity and diabetes, one might expect resistin to exacerbate ischaemia–reperfusion (I/R) injury rather than protect against it (Steppan *et al*., 2001) [3], particularly as resistin counteracts the beneficial effects of insulin, a recognised cardioprotective agent (Hausenloy & Yellon, 2009) [28]. Indeed, in a recent study in Langendorff perfused rat heart, resistin, administered as a preconditioning agent, was found to worsen cardiac I/R injury, as reflected by impaired functional parameters and elevated tissue output of natriuretic peptides, creatine kinase and tumour necrosis factor-α , although infarct size was not determined (Rothwell *et al*., 2006) [29].

Regarding the sex difference, the finding of the current study was in agreement with other studies which had been shown that resistin concentrations were significantly higher in women compared to men (Tuttolomondo *et al*., 2010 ; Yannakoulia *et al*.,2003) [30, 31]. However, it remains to be elucidated whether the sexual dimorphism of body fat distribution or differences in sex steroids are responsible for the observed differences in resistin levels.

In addition our study revealed significant negative correlation between serum resistin level and adiponectin level in the patients group. Adiponectin is a peptide hormone secreted by adipocytes, shown to have a number of beneficial effects, such as antiatherosclerosis and anti-inflammatory properties, and improvement of insulin resistance in the general population [32].In consistent with current study, a significant inverse correlation between serum adiponectin and resistin levels has also been reported in the literatures [33, 34]. It has been reported that those with highest increases of adiponectin also displayed a trend towards a decline in resistin levels [34]. Both hypoadiponectinemia and hyperresistinemia were also positively correlated with hypertension and previous cerebrovascular disease (transient ischemic attack / ischemic stroke) [30].

Furthermore, both hypoadiponectinemia and hyperresistinemia were associated with hypertension [35] and may have prognostic significance for future cardiovascular events in patients with masked hypertension [36]. Elevated resistin opposed to adiponectin plasma levels was proposed to be a strong predictive factor for the occurrence of major adverse cardiac events in patients with stable multivessel coronary artery disease over 1-year follow up [37]. Thus, the balance of the opposite effects of adiponectin and resistin at the level of the endothelial cell may be an important determinant of endothelial dysfunction, and in turn the progress of atherosclerosis. Miyamoto et al. found that resistin may increase the susceptibility of metabolic syndrome by modulating adiponectin secretion from adipocytes [38].

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