

Prognostic value of serum resistin levels in patients with acute myocardial infarction

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Abstract

Background: Resistin is a novel adipokine that is suggested to be involved in inflammatory conditions and atherosclerosis.

Aim: To investigate the prognostic importance of resistin in acute myocardial infarction (AMI) patients.

Methods: Resistin levels were measured in a population of 132 patients with AMI, of whom 72 (54%) had a diagnosis of ST elevation myocardial infarction (STEMI), and 60 (46%) had non-ST elevation myocardial infarction (NSTEMI). Thirty-three consecutive subjects who were referred to elective coronary angiography due to chest pain evaluation with normal coronary angiograms served as controls. All patients were followed-up for the occurrence of major adverse cardiac events (MACE).

Results: There was a significant increase in serum resistin levels in patients with AMI compared to controls (3.71 ± 4.20 vs. 2.00 ± 1.05 , $p = 0.001$, respectively). However, serum resistin levels were similar in patients with STEMI and NSTEMI. (4.26 ± 5.11 vs. 3.06 ± 2.64 , $p = 0.49$, respectively). The patients with MACE had significantly higher levels of serum resistin levels compared to either the AMI or the control group (6.35 ± 5.47 , $p = 0.005$, respectively). Logistic regression analysis revealed that resistin, left ventricular ejection fraction, and coronary artery bypass graft were independent predictors of MACE in AMI patients (OR = 1.11, 95% CI 1.01–1.22, $p = 0.03$ and OR = 3.84, 95% CI 1.26–11.71, $p = 0.018$, respectively).

Conclusions: Serum resistin level was increased in patients with AMI and constituted a risk factor for MACE in this group.

Key words: acute myocardial infarction, resistin, mortality

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INTRODUCTION

The adipose tissue is an active secretory organ, releasing a number of bioactive molecules such as leptin, adiponectin, tumour necrosis factor, plasminogen activator inhibitor type 1 and resistin.

Resistin is a recently described novel adipokine that has been suggested to play a role in the development of insulin resistance and obesity [1]. It is known that inflammation and endothelial dysfunction play a critical role in plaque destabilisation and vulnerability. Inflammatory responses stimulates resistin secretion and resistin could also promote production of proinflammatory mediators such as interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α), and IL-12, and hence aggravate the proinflammatory response [2].

Resistin also activates endothelial cells to up-regulate the expression of endothelin-1, adhesion molecules and chemokines. It induces the expression of matrix metalloproteinases and increases CD40 ligand signalling by down-regulating the TNF receptor-associated factor-3 [3, 4]. These pro-inflammatory mediators have already been implicated in plaque instability. In addition, resistin could also promote lipid accumulation in macrophages [5]. Therefore, resistin may have a role in atherosclerosis progression, and can act as a plaque destabiliser contributing to the occurrence of acute myocardial infarction (AMI) [6].

The aim of this study was to assess the serum resistin level in patients with AMI and to determine its prognostic role for an occurrence of major adverse cardiac events (MACE) in long-term follow-up.

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METHODS

Study population

We enrolled 205 consecutive patients with a diagnosis of AMI (myocardial infarction with ST elevation on ECG [STEMI] and myocardial infarction without ST elevation on ECG [NSTEMI]) between January and June 2011. The final cohort consisted of 132 patients and 32 control subjects after excluding patients who did not meet inclusion criteria. Criteria for the diagnosis of STEMI and NSTEMI were based on the European Society of Cardiology/American College of Cardiology's redefinition of MI guidelines [7]. The local ethical committee had approved the study protocol, and all the patients had signed a consent form.

We excluded patients who had valvular heart disease, heart failure, hepatic or renal dysfunction, evidence of active infective or neoplastic conditions, chronic inflammatory diseases (including rheumatoid arthritis, osteoarthritis, inflammatory bowel disease), major surgery or trauma, type 1 diabetes mellitus (DM) or those who were taking thiazolidinediones or insulin. None of the subjects, either in the investigated or the control group, presented obesity.

The final study population consisted of 132 patients with AMI, where 72 (54%) had a diagnosis of STEMI, and 60 (46%) had NSTEMI. All the patients underwent coronary angiography. Patients received oral aspirin, clopidogrel, and heparin. Allocation of reperfusion therapy was determined by the attending physician and interventional cardiologist. Unless contraindicated or not tolerated, patients were required to have received treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers within 48 h after AMI. One hundred and one of the patients with AMI underwent invasive treatment (percutaneous coronary intervention — PCI). The serum resistin levels were measured from blood taken immediately before the procedure.

Thirty-three consecutive subjects who were referred to elective coronary angiography due to chest pain evaluation with normal coronary angiograms served as controls.

All individuals were subjected to full history taking, clinical examination, and anthropometric measurement of weight and height with the estimation of body mass index (BMI). DM was defined as clinically known or treated DM. Patients were diagnosed as hypertensive if they were documented to have a blood pressure greater than 140/90 mm Hg on two or more occasions, or if they were already on antihypertensive therapy. Each patient underwent serial ECG recording and echocardiographic examination. Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method from apical four-chamber and two-chamber views.

Serial creatine kinase myocardial isoform tests were carried out at baseline, and at six, 12 and 24 h. Other laboratory investigations included serum lipid profile, troponin I, lactate dehydrogenase enzyme, fasting blood glucose, plasma creatinine, plasma fibrinogen, high sensitive C-reactive protein

(hsCRP), pro-B-type natriuretic peptide (proBNP) and glycosylated haemoglobin.

Samples for the evaluation of serum resistin levels were collected at baseline when the patients were initially examined in the emergency room before any treatment was started.

Resistin assay, using ELISA for the quantitative determination of resistin hormone, was supplied by Ray Biotech. Inc. This method of assay employs an antibody specific for the human resistin coated on a well plate. All samples were assayed in duplicate, and the mean of these two measurements was used for analysis.

Mean follow-up of the study population was 9 ± 3 months. MACE were defined as reinfarction, coronary revascularisation, rehospitalisation for any cardiac reason, and cardiovascular mortality. We explored medical records and telephone contacts were established for investigating MACE rates.

Statistical analysis

Statistical analysis was done by SPSS statistical software (SPSS for windows 16.0, Inc., Chicago, IL, USA). Data was tested for normal distribution using the Kolmogorov-Smirnov test. The Kruskal-Wallis nonparametric analysis of variance test was used to perform statistical comparison between groups. Normally distributed continuous variables were compared with t test and parametric data were compared with χ^2 test. The risk factors for cardiovascular mortality were analysed with logistic regression. The covariates were resistin, LVEF, heart rate, urea and coronary artery bypass graft (CABG) history. Data was expressed as mean \pm standard deviation. Statistical significance was defined as $p < 0.05$.

RESULTS

There was no significant difference in age, gender and BMI, among the studied groups. Demographic features of the study population are summarised in Table 1. The control group was younger (53.9 ± 9.2 vs. 58.7 ± 12.1 years, $p = 0.017$). HbA1c, white blood cell, proBNP levels and hsCRP levels were significantly higher in patients with AMI compared to controls, as expected (Table 2). But high density lipoprotein levels of the patient group were significantly lower than in the controls.

There was a significant increase in serum resistin levels in patients with AMI compared to controls (3.71 ± 4.20 vs. 2.00 ± 1.05 , $p = 0.001$, respectively). However, serum resistin levels were similar in patients with STEMI and NSTEMI (4.26 ± 5.11 vs. 3.06 ± 2.64 , $p = 0.49$, respectively). Resistin levels higher than 4.0 ng/mL predicted MACE with 38% sensitivity and 73% specificity.

There were 32 MACE in the follow-up period of 9 ± 3 months. There were seven in-hospital deaths due to cardiogenic shock. MACE were analysed only in patients with AMI. Three patients were lost to follow-up. Among the patients, 13 cardiovascular mortality, nine revascularisations,

Table 1. Demographic data of the study population

	AMI (n = 132)	Controls (n = 32)	P
Age [years]	58.7 ± 12.1	53.9 ± 9.2	0.017
Gender (female)	35 (27%)	18 (56%)	0.003
Hypertension	77 (58%)	20 (63%)	0.694
Diabetes mellitus	43 (33%)	11 (34%)	0.793
Smoking (no/ex/current)	71 (54%)	2 (6%)	< 0.001
Body mass index [kg/m ²]	27.4 ± 4.2	28.6 ± 4.4	0.152
ACE inhibitor	118 (96%)	25 (78%)	0.135
Beta-blocker	123 (93%)	10 (31%)	< 0.001
Statin	129 (98%)	17 (53%)	< 0.001

ACE — angiotensin converting enzyme; AMI — acute myocardial infarction

Table 2. Laboratory values of the study population

	AMI (n = 132)	Controls (n = 32)	P
Total cholesterol [mg/dL]	186.4 ± 47.3	199.1 ± 62.5	0.205
LDL [mg/dL]	119.4 ± 40.2	115.1 ± 22.8	0.561
HDL [mg/dL]	38.6 ± 10.4	45.1 ± 10.9	0.003
Triglyceride [mg/dL]	181.3 ± 140.3	163.8 ± 80.9	0.499
RBC [$\times 10^6/\mu\text{L}$]	4.2 ± 0.8	4.4 ± 0.4	0.399
MPV [fL]	11.2 ± 26	8.2 ± 0.9	0.522
Glucose [mg/dL]	127 ± 45	123 ± 24	0.612
HbA1c [%]	6.8 ± 1.8	5.8 ± 0.5	< 0.001
Pro-BNP [pg/mL]	348.8 ± 441.7	94.8 ± 83.4	< 0.001
hsCRP [mg/L]	25.3 ± 36.7	1.5 ± 0.9	< 0.001
CK-MB [IU/L]	105.5 ± 109.8	Not done	N/A
Troponin I [ng/mL]	19.1 ± 19.9	Not done	N/A
Resistin [ng/mL]	3.71 ± 4.2	2.00 ± 1.05	0.001

LDL — low-density lipoprotein; HDL — high-density lipoprotein; RBC — red blood cell; MPV — mean platelet volume; Pro-BNP — pro-B-type natriuretic peptide; hsCRP — high sensitive C-reactive protein; CK-MB — creatine kinase-myocardial isoform

eight reinfarctions and two rehospitalisations were observed. Serum resistin, urea levels and heart rate were significantly higher, whereas mean LVEF at discharge was significantly lower, in patients with MACE. The patients with MACE had significantly higher levels of serum resistin levels compared to either the AMI or the control group (6.35 ± 5.47 , $p = 0.005$, respectively) (Table 3). Logistic regression analysis revealed that resistin, LVEF and CABG were independent predictors of MACE in AMI patients (OR = 1.11, 95% CI 1.01–1.22, $p = 0.03$ and OR = 3.84, 95% CI 1.26–11.71, $p = 0.018$, respectively) (Table 4).

DISCUSSION

The principal finding of this study is the association of high baseline serum resistin levels with an increased risk of MACE. Resistin was found to be an independent risk factor for predicting MACE in patients with AMI.

A study by Reilly et al. [8] reported that serum resistin levels were correlated with inflammation and coronary atherosclerosis. They also found that serum resistin levels were strongly and independently correlated with TNF- α system activation and IL-6, being consistent with the literature [9]. Both TNF- α and IL-6 are derived from adipose tissue as well as macrophages, and increased levels of these inflammatory cytokines have been linked to obesity, insulin resistance, and atherosclerotic cardiovascular disease [10].

These pro-inflammatory mediators have already been implicated in plaque instability. Therefore, it is considered as an inflammatory marker of atherosclerosis in humans and may represent a novel link between metabolic signals, inflammation and atherosclerosis [8, 11]. Collectively, the above observations suggest that resistin may have a role in accelerating atherosclerosis and acts as a destabilising agent contributing to the occurrence of AMI [6].

Table 3. Resistin levels according to major adverse cardiac events (MACE)

	MACE (+) N = 32	MACE (-) N = 100	P
Female (no)	11 (34%)	24 (24%)	0.247
Hypertension (no)	23 (72%)	54 (54%)	0.074
Diabetes mellitus (no)	13 (41%)	30 (30%)	0.216
Hyperlipidaemia (no)	9 (28%)	25 (25%)	0.725
Family history (no)	9 (28%)	43 (43%)	0.134
Smoker (no)	17 (53%)	54 (54%)	0.931
Atrial fibrillation (no)	0 (0%)	2 (2%)	0.573
PCI (no)	22 (69%)	79 (79%)	0.234
CABG (no)	9 (28%)	13 (13%)	0.04
LVEF [%]	38 ± 12	45 ± 9	0.001
Heart rate [bpm]	91.9 ± 25.3	82 ± 16.1	0.01
Urea [mg/dL]	23.6 ± 12.4	18.8 ± 8.5	0.015
Resistin [ng/mL]	5.06 ± 6.11	3.2 ± 3.3	0.037

PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft; LVEF — left ventricular ejection fraction

Table 4. Predictors of major adverse cardiac events by logistic regression analysis

	Odds ratio	95% confidence interval	P
Resistin [ng/mL]	1.1	1.01–1.22	0.03
Heart rate [bpm]	1.01	0.98–1.04	0.486
Urea [mg/dL]	1.04	0.99–1.09	0.095
Ejection fraction [%]	0.94	0.90–0.99	0.02
Coronary artery bypass graft	3.84	1.26–11.71	0.018

In human studies, the relationship of circulating resistin to BMI, insulin sensitivity, and type 2 DM had been inconsistent [12, 13]. In our work, we found that serum concentrations of resistin were not associated with BMI, parameters of glucose, and lipid metabolism, which indicates that the effect of resistin is independent of BMI and glycaemic and lipid metabolism.

There is controversy regarding resistin levels with several clinical variables. Degawa-Yamauchi et al. [14] found a weak correlation between plasma serum resistin and BMI, whereas Silha et al. [15] reported that resistin concentrations were not correlated with BMI, although the concentrations were correlated significantly with HOMA-IR. Furthermore, Kręcki et al. [16] did not observe any correlation between MACE and resistin levels, whereas Momiyama et al. [17] showed a correlation with resistin levels higher than 4.0 ng/mL with MACE in patients undergoing elective PCI.

A study by Lee et al. [18] showed that high serum resistin levels were dependent predictors for all-cause mortality in patients with AMI. In contrast, in our study, logistic regression

analysis revealed that resistin was an independent predictor of MACE in AMI patients. In the present study, we also found that the initial resistin levels were higher in patients with AMI who were admitted to the hospital. These findings may all support the putative role of resistin in the process of inflammation related to endothelial injury or dysfunction.

Limitations of the study

Patients with type 2 DM were not excluded, which has an influence on adipocytokine levels. Impaired glucose tolerance was not measured either. We compared patients with AMI to a control group. However, a comparison with stable angina pectoris patients would supply greater insight into the hypothesis.

CONCLUSIONS

Serum resistin level was increased in patients with AMI and constituted a risk factor for MACE in this group. To the best of our knowledge, this is the second prospective study reporting an association between resistin levels and MACE in patients with AMI. However, the normal range of resistin levels and an association between resistin and atherosclerosis remains controversial. Thus, the value of resistin levels in risk stratification and follow-up of patients with AMI should be confirmed by large-scale prospective studies.

Conflict of interest: none declared

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Wartość prognostyczna stężenia rezystyny w surowicy u chorych z ostrym zawałem serca

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Streszczenie

Wstęp: Rezystyna jest nową adipokina, która prawdopodobnie uczestniczy w procesach zapalnych i rozwoju miażdżycy.

Cel: Celem niniejszego badania była ocena wartości prognostycznej rezystyny u chorych z ostrym zawałem serca (AMI).

Metody: Zmierzono stężenia rezystyny w populacji złożonej ze 132 chorych z AMI, spośród których u 72 (54%) osób rozpoznano zawał serca z uniesieniem odcinka ST (STEMI), a u 60 (46%) — zawał serca bez uniesienia odcinka ST (NSTEMI). Grupę kontrolną stanowiło 33 kolejnych pacjentów skierowanych na angiografię wieńcową w trybie planowym z powodu bólu w klatce piersiowej, u których wykazano prawidłowy obraz tętnic wieńcowych. Wszystkich chorych obserwowano pod kątem wystąpienia poważnych niepożądanych zdarzeń sercowych (MACE).

Wyniki: U pacjentów z AMI stwierdzono istotne zwiększenie stężenia rezystyny w surowicy w porównaniu z osobami z grupy kontrolnej (odpowiednio $3,71 \pm 4,20$ vs. $2,00 \pm 1,05$; $p = 0,001$). Jednak u chorych ze STEMI i NSTEMI stężenia rezystyny były podobne (odpowiednio $4,26 \pm 5,11$ vs. $3,06 \pm 2,64$; $p = 0,49$). U pacjentów z MACE stężenia rezystyny w surowicy ($6,35 \pm 5,47$; $p = 0,005$) były istotnie wyższe niż u chorych z AMI i osób z grupy kontrolnej. W analizie regresji logistycznej wykazano, że stężenie rezystyny, frakcja wyrzutowa lewej komory i pomostowanie aortalno-wieńcowe były niezależnymi czynnikami predykcyjnymi MACE u chorych z AMI (odpowiednio: OR = 1,11; 95% CI 1,01–1,22; $p = 0,03$ i OR = 3,84; 95% CI 1,26–11,71; $p = 0,018$).

Wnioski: Stężenie rezystyny w surowicy było zwiększone u chorych z AMI i stanowiło czynnik ryzyka MACE w tej grupie chorych.

Słowa kluczowe: ostry zawał serca, rezystyna, śmiertelność

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