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Resistin increases with obesity and atherosclerotic risk factors in patients with myocardial infarction

Katarzyna Piestrzeniewicz[a,*], Katarzyna Łuczak[a], Jan Komorowski[b], Marek Maciejewski[a], Joanna Jankiewicz Wika[b], Jan Henryk Goch[a]

[a]*Ist Department of Cardiology, Medical University of Łódź, Poland*
[b]*Department of Endocrinology, Medical University of Łódź, Poland*

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Abstract

The objective of the study was to assess the relation of resistin to the anthropometric parameters, metabolic risk factors, and C-reactive protein (CRP) in men with myocardial infarction. Subjects were 40 obese (age, 53.6 ± 7.39 years; body mass index, ≥30 kg/m^2) and 40 lean (age, 54.4 ± 6.62 years; body mass index, <25 kg/m^2) men with first acute myocardial infarction. Waist and hip circumferences, CRP, uric acid, fasting glucose, lipid profile, and blood resistin concentration were measured. In obese patients, triglycerides, fasting glucose, and CRP were significantly higher whereas high-density lipoprotein cholesterol was lower than in lean patients. The range of blood resistin concentration was 6.0 to 70.5 ng/mL: 27.84 ± 12.15 ng/mL in obese subjects and 17.35 ± 11.08 ng/mL in lean subjects ($P < .0001$). Significant positive correlation was revealed between blood resistin concentration and each of the analyzed anthropometric parameter and with fasting glucose, low-density lipoprotein cholesterol, and CRP, whereas negative relation was observed between resistin and high-density lipoprotein cholesterol. As revealed by univariate logistic regression analysis, risk of blood resistin concentration being greater than the median value (19.75 ng/mL) was increased by obesity, high-density lipoprotein cholesterol <40 mg/dL, hypertension, and CRP. In multivariate model, independent variables associated with higher median of resistin were obesity and CRP. Obesity increased 5.5-fold the probability of blood resistin concentration being greater than 19.75 ng/mL, whereas each 1-mg/dL increase in CRP increased this probability by 13%. In patients with acute myocardial infarction, obesity is positively related to blood resistin concentration. Resistin is likely to play a major role in the atherogenesis and its complications, and this action seems to be mostly related to the inflammatory reaction.

1. Background

It has become clear recently that adipose tissue is an active endocrine organ, which secretes a large number of bioactive proteins—adipocytokines. These include resistin, which on the grounds of the initial experimental studies was named for its ability to promote insulin resistance. The studies in humans analyzing the relationship between plasma resistin and resistin gene expression in adipocytes and obesity, insulin resistance, and type 2 diabetes mellitus remain controversial [1-6]. In contrast to rodents in which resistin is derived almost exclusively from fat tissue [1], in humans, peripheral blood mononuclear cells seem to a be a major source of this molecule [7,8]. Because obesity is associated with a low-grade inflammation [9,10], it has been suggested that higher levels of resistin expression in adipose tissue might be due to the increased macrophage population infiltrating fat rather than to the adipose cells themselves [11]. Still, it seems that adipocyte-derived resistin is not negligible because it is secreted from preadipocytes and adipocytes independently of the presence of mononuclear blood cells [12]. It has been shown that this molecule may induce endothelial dysfunction, up-regulate adhesion molecules, and promote smooth muscle cell proliferation [13-16] and is related to local and generalized inflammation [6,9,17-22]. That is why a potential role of resistin in early atherogenesis and its late complications responsible for coronary heart disease and myocardial infarction has been suggested [21-24].

The aim of the study was to assess the relation of blood resistin concentration to the anthropometric parameters, metabolic risk factors, and C-reactive protein (CRP) in men with acute myocardial infarction (AMI).

* Corresponding author. Tel.: +48 42 6364471; fax: +48 42 6364471.
E-mail address: kpiestrzeniewicz@gazeta.pl (K. Piestrzeniewicz).

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2. Methods

2.1. Study population

From the cohort of patients with first AMI, successfully treated with primary percutaneous coronary intervention (Thrombolysis in Myocardial Infarction flow grade 3, residual stenosis <30%), 40 obese men aged ≤65 years were selected for the study. Forty lean men matched to the obese group for age and localization of AMI were included in the study as a control group. Patients were designated as obese at body mass index (BMI) ≥30 kg/m^2 and lean at BMI <25 kg/m^2.

Diabetic patients treated with insulin and patients with liver or kidney deficiency (glomerular filtration rate [GFR] <60 mL/min per 1.73 m^2) and abnormal thyroid function were excluded from the study. Additional exclusion criteria were applied because of the requirements of echocardiographic examination performed for the unreported part of this study analysis of left ventricular systolic and diastolic function. These conditions were atrial fibrillation, atrioventricular or bundle-branch block, temporary or permanent stimulation, and significant valvular heart disease.

2.2. Anthropometric measurements clinical definitions and treatment

Diagnosis of AMI was based on the clinical symptoms, electrocardiographic signs, and elevation of myocardial necrotic markers. All patients received aspirin, and those who underwent stenting were concomitantly treated with an additional antiplatelet agent. Heparin was infused during the procedure. Glycoprotein IIb/IIIa inhibitor was administered in a similar proportion of patients from both groups. Anthropometric measurements were made while the subjects were fasting. Body mass index calculated as the body weight divided by height squared (kilograms per square meter) was used as a marker of obesity. Waist circumference was measured at the widest diameter between the xiphoid process of the sternum and the iliac crest, and hip circumference was measured at the widest diameter over the greater trochanters. Waist-to-hip ratio was then calculated. Systolic and diastolic blood pressure was measured before blood sampling.

The study was approved by the Internal Ethics Committee of Medical University of Łódź, and each patient gave an informed consent.

2.3. Laboratory measurements

Along with several analyses performed from the samples of blood taken at the admission to the hospital, CRP and uric acid were assessed. Fasting glucose, lipid profile, and resistin were determined from the blood drawn on the following day. Plasma triglycerides (TG) and total cholesterol (TCH) were measured by enzymatic methods. High-density lipoprotein cholesterol (HDL-CH) was precipitated using dextran sulphate and measured enzymatically. The low-density lipoprotein cholesterol (LDL-CH) was calculated using the Friedewald equation: LDL-CH = TCH − (TG/5) − HDL-CH. Abnormal lipid metabolism was identified as hypercholesterolemia (TCH >200 mg/dL and LDL >100 mg/dL), hypertriglicerydemia (TG >150 mg/dL), and low HDL-CH (HDL-CH <40 mg/dL). Creatinine was measured by enzymatic method. Creatinine clearance was calculated with the abbreviated MDRD equation [25]. Plasma glucose concentrations were measured with the glucose oxidase method, uric acid with the colorimetric method, and CRP with the immunoturbidimetric assay. Fasting blood samples for measurements of resistin were taken on the next day after admission, and plasma was frozen at −70°C until analysis with the quantitative sandwich enzyme immunoassay technique (enzyme-linked immunosorbent assay) obtained from R&D Systems (Minneapolis, MN).

2.4. Statistical analysis

Descriptive statistics are expressed as mean ± SD. Variables were log-transformed before statistical analysis if necessary. Comparisons between the 2 groups were performed using the 2-tailed, nonpaired Student *t* test or Mann-Whitney test, as appropriate. Categorical variables are presented as number and percentage of patients, and comparisons between analyzed groups were analyzed with the χ^2 test. The relationship between resistin concentration and the analyzed parameters (clinical, anthropometric, and biochemical) was examined using Pearson or Spearman correlation coefficient, as appropriate. Univariate and multivariate logistic analysis was performed to identify independent predictors of higher blood resistin concentration (median, 19.75 ng/mL). The results are presented as odds risk (OR) and 95% confidence intervals (CIs). A *P* value less than .05 was considered to be statistically significant. Statistical analysis was performed using Statistica software (version 5.0, StatSoft, Tulsa, OK).

3. Results

Clinical characteristics, anthropometric measurements, and mean values of biochemical parameters of the obese and lean patients are shown in Table 1. History of angina, hypertension, diabetes, smoking, and hypercholesterolemia was similar in both groups. In the obese patients, systolic blood pressure and all the assessed anthropometric measurements (BMI, waist circumference, waist-to-hip ratio) as well as the proportion of patients with hypertriglicerydemia and low HDL-CH were significantly higher than those in the control group. No significant difference in pharmacological treatment before AMI between the study groups was noted. Values of fasting glucose, TG, and CRP were significantly higher in obese than in lean patients, whereas HDL-CH levels were lower. The range of fasting plasma resistin concentration was 6.0 to 70.5 ng/mL. Obese patients had about 1.5-fold higher blood resistin concentrations than lean subjects (27.84 ± 12.15 ng/mL vs 17.35 ± 11.08 ng/mL,

Table 1
Baseline characteristics of the study groups

	Obese (n = 40)	Lean (n = 40)	P
Age	53.6 ± 7.39	54.4 ± 6.62	NS
History of angina	16 (40%)	17 (42.5%)	NS
Smoking	25 (62.5%)	27 (67.5%)	NS
Hypertension	25 (62.5%)	18 (45%)	NS
Systolic blood pressure (mm Hg)	124.1 ± 9.32	119.0 ± 13.2	<.05
Diastolic blood pressure (mm Hg)	75.5 ± 6.18	73.1 ± 8.37	NS
Diabetes mellitus	11 (27.5%)	7 (17.5%)	NS
Hypercholesterolemia	27 (67.5%)	26 (65%)	NS
Hypertriglyceridemia	24 (60%)	13 (32.5%)	<.05
Low HDL-CH	15 (37.5%)	5 (12.5%)	<.01
Treatment before AMI			
Aspirin	14 (35%)	15 (37.5%)	NS
Statin	14 (35%)	12 (30%)	NS
ACEI	20 (50%)	12 (30%)	NS
β-Blocker	14 (35%)	10 (25%)	NS
Sulfonylureas	5/11 (45%)	6/7 (85%)	NS
Biguanides	8/11 (73%)	2/7 (28.5%)	NS
BMI (kg/m^2)	32.2 ± 1.96	23.6 ± 1.40	<.0001
Waist circumference (cm)	111.9 ± 7.52	88.1 ± 7.09	<.0001
Waist-to-hip ratio	1.03 ± 0.05	0.96 ± 0.03	<.001
Fasting glucose (mg/dL)	110.1 ±14.5	94.8 ± 10.3	<.001
TCH (mg/dL)	224.2 ± 44.0	216.7 ± 40.1	NS
LDL-CH (mg/dL)	146.3 ± 43.1	138.4 ± 42.5	NS
TGs (mg/dL)	161.3 ± 59.8	132.9 ± 52.1	<.01
HDL-CH (mg/dL)	45.6 ± 11.9	51.6 ± 12.3	<.05
CRP (mg/dL)	7.95 ± 7.29	4.25 ± 4.84	<.01
Uric acid (mg/dL)	6.11 ± 1.48	5.66 ± 1.47	NS
Creatinine (mg/dL)	0.93 ± 0.17	0.97 ± 0.16	NS
GFR (mL/min per 1.73m^2)	94.42 ± 18.89	88.01 ± 15.82	NS

NS indicates not significant; ACEI = angiotensin-converting enzyme inhibitor.

$P < .0001$) (Fig. 1). Blood resistin concentration that was greater than the median value (19.75 ng/mL) was detected in 40 patients (50% of the whole study group), significantly more often in obese (29 patients, 72.5%) than in lean subjects (11 patients, 27.5%; $P < .0001$).

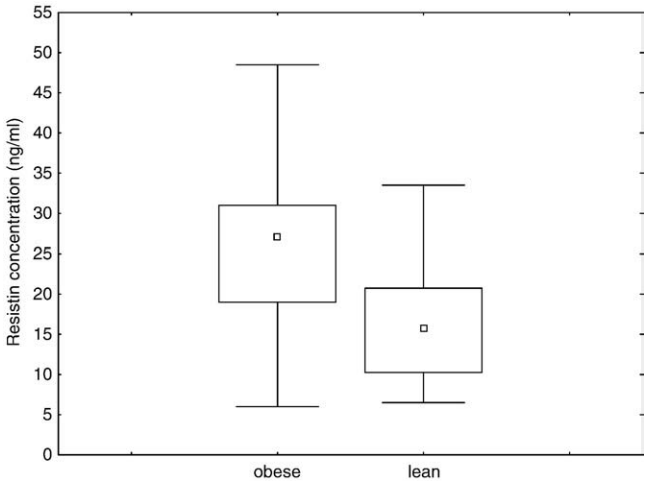

Fig. 1. The mean value of plasma resistin concentration in obese and lean patients. Box plots display median, 25th and 75th percentile, and the extreme values.

Table 2
Correlation between plasma resistin concentration and clinical and biochemical parameters

	r	P
Age	−0.13	NS
Body mass index	0.48	<.0001
Waist circumference	0.50	<.0001
Waist-to-hip ratio	0.42	<.0001
Systolic blood pressure	0.12	NS
Diastolic blood pressure	0.12	NS
Fasting glucose	0.26	<.05
TCH	0.12	NS
HDL-CH	−0.24	<.05
LDL-CH	0.25	<.05
TGs	−0.01	NS
CRP	0.33	<.01
Uric acid	0.07	NS
GFR	−0.17	NS

In the whole study group (Table 2), blood resistin concentration was positively related to each of the analyzed anthropometric parameters, most significantly with waist circumference and also with CRP, LDL-CH, and fasting glucose. A negative correlation between resistin and HDL-CH was observed.

As revealed by univariate logistic regression analysis, the risk of blood resistin concentration being greater than 19.75 ng/mL was 7-fold higher for obesity, 4-fold higher for low HDL-CH, and 2.5-fold higher for hypertension (Table 3). Increase in CRP by each 1 mg/dL increased this risk by 17%. In multivariate model, independent variables associated with higher median of resistin were obesity and CRP. Body mass index ≥30 kg/m^2 increased 5.5-fold the risk of blood resistin concentration being greater than 19.75 ng/mL, whereas each 1-mg/dL increase in CRP increased this probability by 13%. These relations were not significantly changed after adjustment for diabetes: there was a 5.7-fold increase in the risk of

Table 3
Univariate and multivariate logistic regression analysis for median of resistin concentration

	OR	−95% CI	+95% CI	P
Univariate logistic regression analysis for median of resistin				
Age	0.9799	0.9195	1.0442	.5307
History of angina	1.3636	0.5582	3.3312	.4961
Smoking	0.6429	0.2547	1.6228	.3497
Obesity	*6.9504*	*2.6046*	*18.5472*	*.0001*
Diabetes mellitus	1.3333	0.4644	3.8282	.5929
Hypertension	*2.5126*	*1.0186*	*6.1976*	*.0455*
Hypercholesterolemia	0.8942	0.3538	2.2602	.8131
Hypertriglyceridemia	1.6579	0.6835	4.0217	.2635
Low HDL-CH[a]	*4.2000*	*1.3502*	*13.0645*	*.0132*
CRP	*1.1714*	*1.0495*	*1.3074*	*.0048*
Uric acid	1.0642	0.7891	1.4351	.6836
Glomerular filtration rate	0.9893	0.9591	1.0093	.2123
Multivariate logistic regression analysis for median of resistin				
Obesity	5.4585	1.9541	15.2478	.0012
CRP	1.1347	1.0173	1.2657	.0233

[a] HDL-CH <40 mg/dL.

blood resistin concentration being greater than the median value for obesity (OR = 5.69; 95% CI, 2.0137-16.1172; P = .01) and a 15% increase for each 1-mg/dL increase in CRP (OR = 1.15; 95% CI, 1.0261-1.3073; P = .0175).

4. Discussion

The present study concerns association between blood resistin concentration and cardiovascular risk factors in patients with AMI. These results seem to support the opinion of other investigators [21,22,26] that resistin could contribute to the atherogenic process.

Previous reports concerning the potential role of resistin in metabolic disorders are inconsistent. In agreement with Norata et al [27], we have revealed a negative correlation between resistin and HDL-CH. Moreover, HDL-CH <40 mg/dL appeared to be associated with higher median of resistin concentration. An interesting observation was made by Koebnick et al [28] who showed a negative association between resistin and serum apolipoprotein A-1, the major protein of HDL particles. Disparate results come from some other studies showing positive and negative relation between resistin and LDL-CH [17,27,29] as well as no relation between resistin and lipid metabolism [3,14].

Our observation that resistin is positively associated with fasting glucose is consistent with that of Al-Daghri et al [17], Pischon et al [26], and Zhang et al [30]; however, some other investigators show opposite results [3,4,21,22]. Still, the role of resistin in glucose metabolism is open to debate. In experimental studies, blood resistin concentration was positively related to hepatic glucose production [31,32]; and its negative impact on glucose uptake in adipocytes and skeletal muscles has been shown [1,33]. In diabetic patients, resistin was suggested to impair β-cell secretory function, resulting in the increase of blood glucose [30]. Interestingly, in our study, it was hypertension but not diabetes that increased the risk of blood resistin concentration being greater than the median value, although hypertension was not an independent factor. This and previous suggestions of the possible relation between resistin and hypertension and diabetes could be, at least partly, explained by the resistin gene 3′-untranslated region +62G->A polymorphism [34,35].

Human adipocytes were identified as a source of inflammatory cytokines [20]. Resistin was reported to be positively correlated with various inflammatory factors, and inflammation has been identified as a hyperresistinemic state [9]. It has been shown recently that inflammation plays an integral role in the development of cardiovascular disease [23]. Extensive study on CRP has demonstrated that it is associated with atherosclerotic disease [36] and is correlated with traditional risk factors [37,38]. In the study of Pischon et al [26], blood resistin concentration was related to the presence of coronary heart disease in women; and this association was substantially dependent on the CRP levels. On the contrary, Reilly et al [21] showed that predictive value of blood resistin levels in developing atherosclerosis is independent of CRP. Our study confirms the significant relationship between blood concentrations of resistin and CRP, revealed previously in patients with diabetes and coronary artery disease [6,17,19,24], the more so because we have identified CRP as the only biochemical marker associated with blood resistin concentration being greater than the median value of 19.75 ng/mL.

Higher GFR in obese individuals is a phenomenon previously explained by Chagnac et al [39]. The authors argue that the number of nephrons does not increase with the gain of the body fat so that obesity must result in an increase in a single nephron and absolute GFR, and this hyperfiltration is the most evoked mechanism to explain obesity-related nephropathy. In our study, although mean GFR was higher in obese than in lean patients, the difference was not significant, possibly because of the fact that all patients in the obese group were only moderately obese. It has been suggested that resistin correlates with decreasing renal function [24], but such association was confirmed only at GFR less than 60 mL/min per 1.73 m^2 [40]. Indeed, in our study in which renal deficiency was an exclusion criterion, no significant relation between resistin and GFR was revealed; and the risk of blood resistin concentration being greater than 19.75 ng/mL was not affected by GFR.

In our group of patients, blood resistin concentrations were significantly higher in obese than in lean patients and were positively related to anthropometric parameters; and obesity was an independent factor that increased the risk of higher median of resistin. Similar observations were made in several previous studies [2,4]. Disparately, no differences in blood resistin concentrations were found between overweight (BMI $\geq$25 kg/m^2) and lean (BMI <25 kg/m^2) patients by Koebnik et al [28]. Positive association between resistin and BMI was observed only in women by Vilarrasa et al [41]. In some other studies, there was no correlation between serum resistin and various markers of obesity and between adipocyte resistin expression and anthropometric measurements [3,5].

In the present study, in accordance with some previous reports [41], we have not revealed any changes in blood resistin concentrations with aging, although in the study of Koebnick et al [28], a decrease of blood resistin concentration with age was observed. Our study was designed for male subjects to avoid the impact of sex-related differences in the location of the adipose tissue, the number of fat cells, and fat cell size. Moreover, blood resistin concentrations were higher in women than in men [5,28]; and sex-specific relation of resistin with metabolic factors was observed [24].

Disagreements and conflicting data concerning the involvement of resistin in proatherogenic disorders suggest that the possible action of this molecule is not direct but depends on its several bioactivities. The groups of the previously analyzed patients differed in terms of age, presence and intensity of obesity, and coexisting diseases.

Ethnic differences and resistin gene polymorphism are the other possible cofactors. Future investigations including genetic and basic science research are warranted to elucidate the possible pathophysiological role of resistin as a mediator in the signaling pathways.

4.1. Study limitations

Serial analysis of resistin concentration in the course of AMI performed by Lubos et al [42] showed that resistin rises in the course of myocardial infarction and peaks beyond the 12th hour of infarction. However, in our study, the effects of resistin on the atherosclerotic risk factors could have been affected by the acute event, the more so because the time since the onset of symptoms to the blood sampling for resistin measurement exceeded the 12th hour of AMI and differed in individual patients.

Because plasma insulin concentrations were not available in our data set, we were not able to reliably analyze the impact of resistin on glucose metabolism.

5. Conclusions

1. In patients with AMI, obesity is positively related to the blood resistin concentration.
2. Resistin is likely to play a major role in the atherogenesis and its complications, and this action seems to be mostly related to the inflammatory reaction.

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