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Resistin predicts ischemia in myocardial perfusion scintigraphy

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Aim: Resistin plays a role in the pathogenesis of coronary artery disease and is related to mortality and morbidity through a number of mechanisms. We hypothesize that plasma resistin levels are increased in the presence of ischemia, as measured by GATED single-photon emission computed tomography myocardial perfusion scintigraphy (SPECT MPS), in comparison with nonischemic subjects.

Materials and methods: Fasting intravenous blood samples of patients were drawn before a stress test. An ELISA kit was used for the assays. All patients underwent a technetium 99m-sestamibi GATED SPECT MPS study with a 1-day stress-rest protocol. Images were analyzed visually and patients were assessed as ischemic or nonischemic. Resistin levels were presented as medians (25th–75th percentiles) and were compared using the Mann–Whitney U test.

Results: Plasma resistin levels were higher in the ischemic group (n = 47) than in the nonischemic group (n = 67) [9.04 μmol/L (6.27–11.8 μmol/L) vs. 3.56 μmol/L (0.39–7.93 μmol/L), respectively; $P < 0.001$). We showed that plasma resistin levels (OR = 1.26, 95% CI: 1.13–1.41; $P < 0.001$) and METs (OR = 0.82, 95% CI: 0.70–0.92; $P = 0.021$) were independent predictors of ischemia. No linear correlation was found between plasma resistin levels and GATED SPECT or stress test parameters.

Conclusion: Increased baseline resistin levels are independently related to presence of ischemia but are not related to the extent or severity of ischemia, or other functional parameters such as poststress ejection fraction, end systolic, and end diastolic volumes.

Key words: Resistin, myocardial perfusion scintigraphy, ischemia

1. Introduction

Resistin aggravates atherosclerosis through the stimulation of monocytes, endothelial cells, and vascular smooth muscle cells to induce vascular inflammation in humans and animal models (1–3). Serum resistin is a biological marker of coronary artery disease (CAD) and restenosis, especially in patients with type 2 diabetes (4,5).

However, several clinical studies have demonstrated that resistin is an inflammatory cytokine, although not directly related to atherosclerosis, metabolic syndrome, or CAD (6,7). Other studies have shown that serum resistin is correlated with hs-CRP, inflammatory processes, age, and decreased renal function, but is not directly associated with severe coronary stenosis or vascular events (5,8). No relationship has been shown between resistin and type 2 diabetes in Korean patients (9).

As described above, results regarding the clinical importance of resistin are controversial and only one large cross-sectional study has directly evaluated the relationship between resistin and cardiac functional status using stress echocardiography (10). We hypothesize that plasma resistin levels are increased in the presence of ischemia compared with nonischemic subjects when using GATED single-photon emission computed tomography myocardial perfusion scintigraphy (SPECT MPS). Accordingly, this is the second study to report a correlation between resistin and functional status of myocardium, but using a different method.

2. Materials and methods

2.1. Study population

This study included 114 consecutive patients [42 males (36.8%), 72 females (63.2%), mean age 57 ± 11 years] with ischemic (n = 47) and nonischemic (n = 67) results based on GATED myocardial SPECT. None of the patients had cardiac valve disease, cardiomyopathy, malignant

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arrhythmias, acute or chronic liver disease, renal failure, suspected pregnancy, or were breastfeeding at the time of inclusion in the study. Patients with a fixed defect, history of myocardial infarction, bypass, or revascularization were excluded. GATED SPECT MPS was performed to diagnose CAD. A detailed history, including risk factors, current medications, body mass index (BMI), waist circumference, blood pressure before and after exercise test, metabolic equivalents (METs), and baseline heart rate was obtained from all patients. Fasting intravenous (i.v.) blood samples of patients were drawn before the stress test. All patients underwent technetium 99m-sestamibi (99mTc-sestamibi) GATED SPECT MPS study with a 1-day stress-rest protocol. All subjects provided informed consent prior to enrollment in the study and the study was approved by the local ethics committee.

2.2. Imaging protocol

Blood pressure, heart rate, and EKG of the subjects were monitored during the test. Test endpoints were physical exhaustion, anginal complaints, dyspnea, a significant decrease in blood pressure greater than 10 mmHg, or achievement of maximal age-related heart rate. In other patients, a pharmacological stress test was performed by i.v. administration of either adenosine (0.14 mg/kg/min for 6 min) or dobutamine (up to a maximum dose of 40 μg/kg/min in 15 min) until the required age-related heart rate was reached. The test was performed using a 1-day protocol. Beta-blockers and calcium antagonists were discontinued for 48 h and long-acting nitrates were discontinued for 24 h before GATED myocardial SPECT. Caffeine- and theophylline-containing foods/medications and tobacco were discontinued for 1 day prior to the study. At peak exercise, 296–370 MBq (8–10 mCi) of 99mTc-Sestamibi was injected intravenously. Exercise continued for another 1–2 min after injection of the tracer. Resting images were obtained 3–4 h after stress imaging with a 3-fold injection of the tracer. The images were acquired 45 min after stress injection and 60 min after rest injection, with a single-headed gamma camera (E-cam Single Head Gamma Camera, Siemens, Germany) with all-purpose high-resolution collimators. The studies were prefiltered with a Butterworth filter and back-projected with a ramp filter. After reconstruction, the data were displayed as tomographic slices and bull's eye maps (polar plots), and images were visually evaluated. Post-stress GATED parameters [ejection fraction (EF), end systolic/end diastolic volumes (ESV/EDV), and automatic stress defect scores (SDS)] were recorded.

2.3. Resistin measurements

Serum specimens were separated from whole blood samples by centrifugation at 5000 rpm for 10 min and stored at –20 °C until assay time. Hemolytic and lipemic serum samples were excluded from the study. An ELISA kit was used for the assays (BioVendor, Czech Republic), which were performed with the BioTek Epoch microplate reader (BioTek Instruments, Inc. Winooski, VT, USA). Before the assay procedure, all samples were brought to room temperature and mixed carefully to avoid foam development. Standards, controls, dilution buffer as blank, and samples (100 μL each) were added to the wells. The plate was incubated at room temperature for 1 h on an orbital shaker at 300 rpm. Wells were washed 3 times with a wash solution (0.35 μL per well). Biotin-labeled antibody solution (100 μL) was added to each well and the plate was incubated at room temperature for 1 h on an orbital shaker at 300 rpm. After repeating the washing process, streptavidin-HRP (100 μL) was added to each well. The incubation and washing processes were repeated. After these steps, a substrate solution (100 μL) was added to each well. The plate was covered with aluminum foil to avoid sunlight and incubated at room temperature for 10 min. Color development was stopped by adding stop solution (100 μL) to each well. The absorbance of each well was determined by using a microplate reader set to 450 nm with the reference wavelength set to 630 nm. The absorbance at 630 nm was subtracted from that at 450 nm. The standard curve was as predicted and control results were in the appropriate range.

2.4. Statistical analysis

Statistical analyses were performed using the PASW 18 statistical software (version 18.0 for Windows; SPSS Inc., Chicago, IL, USA). Normality analyses of continuous variables were performed with histogram curves. Continuous variables are presented as means ± standard deviation or medians (25th–75th percentiles) and when compared between the 2 groups, an independent samples *t*-test and Mann–Whitney U test were performed. Spearman's test was performed to identify linear correlations between 2 continuous variables. Categorical variables were compared between the 2 groups using chi-square tests and presented as frequencies and percentages. Receiver operating curve (ROC) analyses were performed to determine the cut-off value of resistin levels for estimating ischemia. Univariate and multivariate logistic regression analyses were performed to estimate independent predictors of ischemia based on MPS. A forward stepwise logistic regression method was used and P values less than 0.05 were considered to indicate statistical significance.

3. Results

Patient characteristics are presented in Table 1. Sex distribution was similar in the 2 groups; 21 males (44.7%) in the ischemic group and 21 males (31.3%) in the nonischemic group (P = 0.146). Mean age was 60 ± 10 years in the ischemic group and 55 ± 11 years in the nonischemic

Table 1. Characteristics of the patients.

	Nonischemic patients (n = 67)	Ischemic patients (n = 47)	P
Age (years)	55 ± 11	60 ± 10	**0.015**
Sex (male; n, %)	21 (31)	21 (44)	0.146
Body mass index (kg/m^2)	30.2 ± 4.7	30 ± 4.2	0.841
Hypertension (n, %)	38 (56.7)	30 (63.8)	0.446
Diabetes (n, %)	11 (16.4)	11 (23.4)	0.299
Hyperlipidemia (n, %)	15 (22.4)	11 (23.4)	0.899
Resistin (μmol/L)	3.56 (0.39–7.93)	9.04 (6.27–11.8)	**<0.001**
Current smoking (n, %)	14 (20.9)	10 (21.3)	0.961
Medication (n, %)			
Beta blocker	13(20)	15(31.9)	0.151
Calcium channel blocker	12(18.5)	11(23.4)	0.523
Antiaggregant	15(23.1)	21(44.7)	**0.016**
ACE inhibitor	19(29.2)	9(19.1)	0.224
Digital	0(0)	1(2.1)	0.237
Nitrate	0(0)	6(12.8)	**0.003**
Oral antidiabetic or insulin	8(11.9)	8(17.0)	0.442
Antihyperlipidemic	8(11.9)	8(17.0)	0.442
Systolic blood pressure (mmHg)	124.3 ± 16.8	123.6 ± 15.3	0.819
Diastolic blood pressure (mmHg)	73.5 ± 8.4	73.8 ± 8.0	0.875
Waist circumference (cm)	101.3 ± 10.1	99.7 ± 11.6	0.428

group (P = 0.015). Mean MET levels were 7.9 ± 2.7 in the ischemic group and 10 ± 2.8 in the nonischemic group (P < 0.001). Frequencies of nitrate and antiaggregant use were higher in the ischemic group.

Plasma resistin levels were higher in the ischemic group than in the nonischemic group and median values were 9.04 μmol/L (6.27–11.8 μmol/L) and 3.56 μmol/L (0.39–7.93 μmol/L), respectively (P < 0.001).

There was no linear correlation between plasma resistin levels and both GATED parameters (EF, ESV, and EDV) and stress test (automatically calculated SSS and SDS) parameters (Table 2).

Table 2. Correlations of ADMA levels between both GATED and stress parameters.

	Plasma resistin levels	
	r	P
Stress defect score	–0.041	0.667
Summed difference score	–0.165	0.079
Ejection fraction	0.151	0.128
End systolic volume	–0.108	0.283
End diastolic volume	–0.062	0.537

A 0.80 sensitivity and 0.57 specificity were obtained for a 5.4 μmol/L cut-off value of resistin in ROC analyses (AUC = 0.788; P < 0.001; Figure).

In univariate logistic regression analyses, plasma resistin level (OR = 1.3, 95% CI: 1.2–1.4; P < 0.001), age (OR = 1.04, 95% CI: 1.008–1.082; P = 0.018), and METs (OR = 0.773, 95% CI 0.67–0.90; P = 0.001) were independent predictors of ischemia according to GATED SPECT MPS. In age- and METs-adjusted multivariate analyses, plasma resistin level remained independently related to ischemia (OR = 1.3, 95% CI: 1.1–1.4; P < 0.001). METs were also related to ischemia (OR = 0.82, 95% CI: 0.70–0.97; P = 0.021; Table 3).

4. Discussion

Our results showed plasma resistin levels were higher in the ischemic group, and that an increased resistin level was an independent predictor of ischemia presence when adjusted for age and METs, but did not correlate adequately with severity of ischemia, EF, ESV, or EDV. A 5.4 μmol/L cut-off value for resistin yielded strong sensitivity but moderate specificity.

To date, only one study has reported the functional status of myocardium in stable CAD. The authors measured serum resistin after a treadmill exercise test by performing stress echocardiography. The frequency of inducible ischemia was significantly higher in the highest resistin quartile. After adjusting the model for inflammatory markers, resistin remained associated with inducible ischemia (10). Yaseen et al. grouped elderly patients in ischemic and nonischemic groups, as well as diabetic and nondiabetic groups. Ischemic geriatric patients in both the diabetic and nondiabetic groups had significantly higher plasma resistin levels (11). We also investigated the functional status of myocardium in stable CAD using a different method than GATED MPS. We obtained similar results as in the 2 above-mentioned studies, which indicates that resistin could be an independent predictor of ischemia.

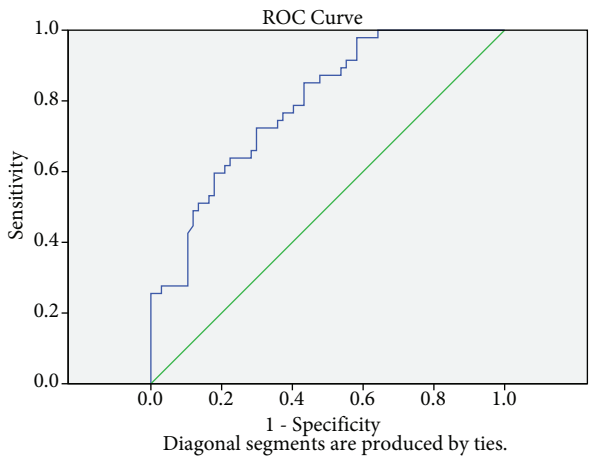

Figure. We obtained a 0.80 sensitivity and 0.57 specificity for cut-off value of resistin of 5.4 in ROC analyses (AUC = 0.788; P < 0.001).

In addition to studies on the functional status of myocardium, others have evaluated the anatomical status of coronary arteries. Kręcki et al. compared resistin levels between 3 vessel diseases and controls; the mean resistin levels were similar in the 2 groups (12). Pilz et al. reported that resistin was not an independent risk factor for angiographic cardiovascular disease (13). Hoefle et al. were in agreement with the last 2 authors and reported no significant increase in plasma resistin levels in coronary stenosis (14). On et al. found higher resistin levels in CAD in type 2 diabetes mellitus (15). In another study, the severity of CAD was represented as the number of stenoses in coronaries. Resistin levels were higher in angiographic CAD, and after adjusting for age and sex, resistin levels remained high, which correlated with the number of stenotic segments; the authors suggested resistin to be related to the presence and severity of the disease (16). In contrast, our results suggest that resistin is related only to the presence of the disease.

Previous studies did not report a resistin cut-off level or related diagnostic value for estimating CAD or ischemic heart disease. We revealed that resistin has a high sensitivity for ischemia when 5.4 μmol/L is used as the cut-off.

In conclusion, increased plasma resistin levels are independently related to the presence of ischemia but not to its extent, severity, or other functional parameters, such as poststress ejection fraction and end systolic/diastolic volumes. An assay of plasma resistin can be considered a highly sensitive test when a cut-off value of 5.4 μmol/L is used.

Table 3. Predictors of ischemia on MPS. (Logistic regression analyses, method: forward stepwise LR).

	Univariate analyses			Multivariate analyses		
	OR	95% CI for OR	P	OR	95% CI for OR	P
Age (year)	1.04	1.01–1.08	0.018	-	-	-
Plasma resistin (μmol/L)	1.28	1.15–1.42	<0.001	1.26	1.13–1.41	<0.001
Metabolic equivalent tasks	0.77	0.67–0.90	0.001	0.82	0.70–0.97	0.021

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