Original Article

Serum Resistin Levels and Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention

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Aim: Resistin is an adipocytokine that may link inflammation and atherosclerosis. We studied the associations of resistin levels with cardiovascular events and restenosis.

Methods: We measured pre-procedural serum resistin levels in 140 patients with coronary artery disease undergoing elective percutaneous coronary intervention (PCI), of whom 97 had a stent. Restenosis was defined as >50% stenosis at follow-up angiography. Patients were followed for 3 years for major adverse cardiovascular events (MACE).

Results: At 8 ± 6 months after PCI, re-angiography was performed in 94 (67%) patients, of whom 42 had restenosis. Between 42 patients with restenosis and 52 without restenosis, resistin (4.5 ± 2.6 vs. 4.5 ± 2.5 ng/mL) and C-reactive protein (CRP) (median 0.70 vs. 0.70 mg/L) levels did not differ. During 3-year follow-up, MACE occurred in 24 patients (1 death, 21 unstable angina, 2 stroke). Compared with 116 patients without MACE, 24 with MACE had higher resistin (5.4 ± 2.4 vs. 4.3 ± 2.5 ng/mL) and CRP (1.30 vs. 0.60 mg/L) levels ($p < 0.05$). Patients with MACE more often had resistin >4.0 ng/mL than without MACE (75% vs. 35%, $p < 0.001$). Resistin correlated with CRP levels ($r = 0.31$). To clarify the association between MACE and resistin, patients were divided into 2 groups by resistin levels. Kaplan-Meier analysis showed a lower event-free survival rate in patients with resistin >4.0 ng/mL than without it ($p < 0.001$). On multivariate analysis, resistin, but not CRP, was an independent predictor of MACE. The hazard ratio for MACE was 3.6 (95%CI = 1.4-9.2) for resistin >4.0 ng/mL.

Conclusion: Serum resistin levels were found to be associated with further cardiovascular events in patients undergoing PCI.

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Key words; Cardiovascular events, Coronary artery disease, Inflammation, Resistin, Restenosis

Introduction

Resistin is an adipocytokine that may link obesity with insulin resistance or diabetes. In 2001, Stepman *et al.*¹⁾ reported that serum resistin levels are elevated in obese mice and decrease upon treatment with

thiazolidinediones; however, subsequent studies in mouse models and human adipocytes produced disparate findings regarding the role of resistin in obesity and insulin resistance^{2, 3)}. Recently, resistin has been suggested to play a role in inflammation and atherosclerosis. In humans, resistin is expressed primarily in inflammatory cells⁴⁾, and resistin expression in monocytes is markedly increased by proinflammatory cytokines⁵⁾. Two studies demonstrated that resistin promotes endothelial cell activation by endothelin-1 release and up-regulates the expression of adhesion molecules, such as VCAM-1 and MCP-1, in cultured endothelial cells^{6, 7)}. Resistin also promotes human

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smooth muscle cell proliferation⁸⁾. Moreover, Burnett *et al.*⁹⁾ reported that resistin mRNA and protein levels are elevated in the aortas of apolipoprotein E-deficient mice and increase during atherosclerosis progression. They also observed abundant resistin proteins in human carotid endarterectomy samples. These findings suggest a potential role of resistin in inflammation and atherosclerosis.

Regarding blood levels of resistin, Burnett *et al.*⁹⁾ showed that 38 patients with coronary artery disease (CAD) have high resistin levels. We also reported that serum resistin levels were higher in 157 patients with stable CAD than in 73 without CAD, and correlated with the severity of CAD¹⁰⁾. Reilly *et al.* showed that resistin levels were associated with increased coronary calcification by computed tomography in 879 asymptomatic subjects¹¹⁾. These observations suggest that resistin plays a role in the development of CAD. Moreover, we¹⁰⁾ and others^{11, 12)} reported that serum resistin levels correlate with plasma C-reactive protein (CRP) levels, thus suggesting a link between resistin and inflammation; however, studies investigating the association between resistin levels and cardiovascular events are scarce. Therefore, the present study was performed to elucidate the associations of pre-procedural serum resistin levels with cardiovascular events and angiographic restenosis in patients with CAD undergoing elective percutaneous coronary intervention (PCI).

Methods

Study Patients

We measured pre-procedural serum resistin levels in 140 consecutive patients with CAD (age 65 ± 9 years; 113 men (81%)) who underwent elective PCI for native coronary stenotic lesions at the National Defense Medical College Hospital from 2000 to 2004. Any patients with acute myocardial infarction, those who had drug-eluting stent implantation, those with a history of coronary artery bypass surgery (CABG), or those with cardiomyopathies or valvular heart disease were excluded; however, 15 patients with unstable angina at rest were included in this study. Our study was approved by the institutional ethics committee. After written informed consent was obtained from all the study patients, overnight-fasting blood samples were taken on the morning of the day that PCI was scheduled.

Serum Resistin and Other Biochemical Analyses

Blood samples were centrifuged at 2000 g for 15 minutes at 4°C. The serum and plasma were frozen and stored at -80°C until analyzed. Serum resistin

levels were measured by an enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (BioVendor Laboratory Medicine Inc., Brno, Czech Republic). All samples were measured in duplicate, and the results were averaged. This kit is highly specific and does not cross-react with leptin, adiponectin or TNF- α . The lower detection limit of this assay was 1.0 ng/mL. The intra- and inter-assay coefficients of variation values were 3% and 6%, respectively. Serum lipid and creatinine levels were measured by standard laboratory methods. Serum insulin levels were measured by a chemiluminescent enzyme immunoassay using a commercially available kit (Chemilumi Insulin, Kyowa, Tokyo). Insulin resistance was evaluated by the homeostasis model assessment for insulin resistance (HOMA-IR)¹³⁾. Plasma high-sensitivity CRP (hsCRP) levels were measured using a BNII nephelometer (Dade Behring, Tokyo, Japan).

Coronary Angiography and Follow-up

Coronary angiograms were recorded using the Judkins technique and the cineangiogram system (Toshiba, Tokyo, Japan). Minimal luminal diameter, reference diameter and percent diameter stenosis were assessed using computerized quantitative angiography. CAD was defined as the presence of at least one coronary artery having >50% luminal diameter stenosis. Of the 140 patients undergoing PCI, 97 (69%) had bare metal stent implantation, mainly because of either a coronary dissection or a suboptimal result (>30% residual stenosis) after angioplasty, and 43 (31%) had only angioplasty; however, the treatment strategy and the selection of balloon catheters and stents depended on the interventionists' discretion. Although all study patients had been instructed to undergo a 6-month follow-up angiography, only 94 (67%) patients underwent re-angiography at 8 ± 6 months after PCI. Angiographic restenosis was defined as >50% luminal diameter stenosis in the segment treated by PCI. All 140 study patients were followed for up to 3 years (25 ± 19 months) for major adverse cardiovascular events (MACE) (death, non-fatal myocardial infarction, hospitalization for rest unstable angina, or stroke). This clinical outcome was evaluated by reviewing the patient medical records supplemented by a telephone interview of the patients and their family.

Statistical Analysis

Differences between 2 groups were evaluated by the unpaired *t* test for parametric variables, by the Mann-Whitney *U* test for nonparametric variables, or by the chi-square test for categorical variables. Correlations between resistin levels and hsCRP or insulin

Table 1. Clinical characteristics of patients with and without restenosis

	Restenosis (–) (<i>n</i> = 52)	Restenosis (+) (<i>n</i> = 42)	<i>p</i> value
Age (years)	64 ± 9	67 ± 7	NS
Gender (male)	41 (79%)	35 (85%)	NS
Body mass index (kg/m ²)	24 ± 4	25 ± 3	NS
Hypertension	30 (58%)	30 (71%)	NS
Systolic blood pressure (mmHg)	132 ± 18	137 ± 18	NS
Hyperlipidemia	28 (54%)	29 (69%)	NS
Total cholesterol (mg/dL)	205 ± 38	201 ± 32	NS
HDL-cholesterol (mg/dL)	50 ± 13	49 ± 12	NS
Diabetes mellitus	17 (33%)	12 (29%)	NS
Fasting insulin levels (μU/mL)	9.8 ± 7.0	9.7 ± 6.2	NS
HOMA-IR	2.7 ± 2.2	2.8 ± 2.1	NS
Current smoking	16 (31%)	4 (10%)	<0.05
Unstable angina	3 (6%)	6 (14%)	NS
Plasma hsCRP levels (mg/L) (median)	0.70	0.70	NS
Serum resistin levels (ng/mL)	4.5 ± 2.5	4.5 ± 2.6	NS

Data are presented as the mean ± SD or the number (%) of patients. Hypertension was defined as blood pressure ≥140/90 mmHg or on medication. Hyperlipidemia was defined as total cholesterol >240 mg/dL or on medication. Diabetes was defined as fasting glucose ≥126 mg/dL or on hypoglycemic drugs or insulin.

levels were evaluated by Spearman's rank correlation test. Forward stepwise multiple logistic regression analysis was used to elucidate any associations between restenosis and resistin or other factors. Event-free survival in patients with and without a resistin level of >4.0 ng/mL was analyzed by the Kaplan-Meier method and was compared by the log-rank test. This cutoff level (>4.0 ng/mL) of resistin was determined using receiver-operating characteristics (ROC) curve analysis. Multivariate Cox proportional hazards regression analysis was used to identify independent predictors of MACE. A *p* value of <0.05 was considered significant. The results are presented as the mean ± SD or the median.

Results

Of the 94 patients who underwent re-angiography at 8 ± 6 months after PCI, 42 (45%) were found to have angiographic restenosis. Of the 42 patients who developed restenosis, 14 were hospitalized for unstable angina. Compared with 52 patients without restenosis, 42 with restenosis had a lower rate of current smoking (10% vs. 31%, *p* < 0.05) (**Table 1**); however, there were no differences in pre-procedural resistin (4.5 ± 2.6 vs. 4.5 ± 2.5 ng/mL) or hsCRP (median 0.70 vs. 0.70 mg/L) levels between patients with and without restenosis (*p* = NS). Regarding angiographic data at PCI (**Table 2**), the reference diameter

was smaller in patients with restenosis than in those without restenosis (*p* < 0.05), but there were no differences in either the prevalence of stent implantation or the medication after PCI between 2 groups. To elucidate independent factors for restenosis, age, gender, hypertension, diabetes, smoking, statin, stent, reference diameter, and resistin and hsCRP levels were entered into a multiple logistic regression model. In multivariate analysis, smoking (odds ratio = 0.2, 95%CI = 0.1–0.9) and the reference diameter (odds ratio = 0.3, 95%CI = 0.1–0.9) were independent predictors of angiographic restenosis (*p* < 0.05), but resistin and hsCRP levels were not.

During 3-year follow-up, MACE occurred in 24 (17%) of 140 patients (1 sudden death, 21 unstable angina, and 2 stroke). Of the 21 patients who developed unstable angina, 14 and 7 were found to have restenosis and de novo stenotic lesions, respectively. Compared with 116 patients without MACE, 24 with MACE were older (70 ± 6 vs. 64 ± 9 yrs, *p* < 0.005), but serum creatinine levels were similar between the 2 groups (**Table 3**). Notably, patients with MACE had higher levels of resistin (5.4 ± 2.4 vs. 4.3 ± 2.5 ng/mL) and hsCRP (1.30 vs. 0.60 mg/L) than those without MACE (*p* < 0.05). Patients with MACE more often had a resistin level of >4.0 ng/mL (75% vs. 35%) and an hsCRP level of >1.0 mg/L (67% vs. 35%) than those without MACE (*p* < 0.01); however, serum resistin levels correlated with age (*r* = 0.20, *p* < 0.05).

Table 2. PCI procedures and medication after PCI in patients with and without restenosis

	Restenosis (–) (<i>n</i> = 52)	Restenosis (+) (<i>n</i> = 42)	<i>p</i> value
Number of > 50% stenotic vessels	1.8 ± 0.7	1.7 ± 0.6	NS
PCI procedures			
Diffuse lesion (> 10 mm)	14 (27%)	10 (24%)	NS
Reference diameter (mm)	3.3 ± 0.7	3.0 ± 0.5	< 0.05
Diameter stenosis before PCI (%)	90 ± 8	91 ± 8	NS
Diameter stenosis after PCI (%)	13 ± 15	17 ± 19	NS
Stent placement	35 (67%)	28 (67%)	NS
Medication after PCI			
Aspirin	50 (96%)	39 (93%)	NS
Ticlopidine	43 (83%)	29 (69%)	NS
Statin	30 (58%)	31 (74%)	NS
ACE inhibitors or ARB	19 (37%)	18 (43%)	NS

Data are presented as the mean ± SD or the number (%) of patients. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers.

Table 3. Clinical characteristics of patients with and without MACE

	MACE (–) (<i>n</i> = 116)	MACE (+) (<i>n</i> = 24)	<i>p</i> value
Age (years)	64 ± 9	70 ± 6	< 0.005
Gender (male)	94 (81%)	19 (79%)	NS
Body mass index (kg/m ²)	24 ± 3	24 ± 3	NS
Hypertension	70 (60%)	19 (79%)	NS
Systolic blood pressure (mmHg)	133 ± 19	135 ± 12	NS
Hyperlipidemia	65 (56%)	12 (50%)	NS
Total cholesterol (mg/dL)	200 ± 38	206 ± 37	NS
HDL-cholesterol (mg/dL)	48 ± 12	51 ± 15	NS
Diabetes mellitus	37 (32%)	9 (38%)	NS
Fasting insulin levels (μU/mL)	10.5 ± 7.8	8.0 ± 3.7	NS
HOMA-IR	2.9 ± 2.4	2.4 ± 1.3	NS
Current smoking	29 (25%)	4 (17%)	NS
Unstable angina	10 (9%)	5 (21%)	NS
History of myocardial infarction	25 (22%)	5 (21%)	NS
Serum creatinine levels (mg/dL)	0.90 ± 0.22	0.92 ± 0.21	NS
Plasma hsCRP levels (mg/L) (median)	0.60	1.30	< 0.01
Serum resistin levels (ng/mL)	4.3 ± 2.5	5.4 ± 2.4	< 0.05
Resistin level > 4.0 ng/mL	41 (35%)	18 (75%)	< 0.001

Data are presented as the mean ± SD or the number (%) of patients.

and hsCRP levels ($r=0.31$, $p<0.001$), but not with insulin levels or HOMA-IR. Regarding angiographic data at PCI (**Table 4**), the number of > 50% stenotic coronary vessels tended to be greater in patients with MACE than in those without MACE, but the prevalence of stent implantation and medication after PCI did not differ between the 2 groups. To clarify the association between MACE and resistin levels, the 140

study patients were divided into 2 groups according to resistin levels. Kaplan-Meier analysis showed a lower event-free survival rate in patients with a resistin level > 4.0 ng/mL than in those without ($p<0.001$) (**Fig. 1**). In multivariate Cox proportional hazards regression analysis, resistin levels were found to be a significant predictor of MACE independent of age, but hsCRP levels were not. The hazard ratio for MACE was 3.6

Table 4. PCI procedures and medication after PCI in patients with and without MACE

	MACE (–) (<i>n</i> = 116)	MACE (+) (<i>n</i> = 24)	<i>p</i> value
Number of > 50% stenotic vessels	1.7 ± 0.7	2.0 ± 0.6	NS
LMT disease	0 (0%)	0 (0%)	NS
PCI procedures			
Diffuse lesion (> 10 mm)	25 (22%)	7 (29%)	NS
Reference diameter (mm)	3.1 ± 0.6	3.0 ± 0.6	NS
Diameter stenosis before PCI (%)	90 ± 8	90 ± 8	NS
Diameter stenosis after PCI (%)	14 ± 17	14 ± 16	NS
Stent placement	83 (72%)	14 (58%)	NS
Medication after PCI			
Aspirin	111 (96%)	22 (92%)	NS
Ticlopidine	90 (78%)	17 (71%)	NS
Statin	79 (68%)	14 (58%)	NS
ACE inhibitors or ARB	47 (41%)	14 (58%)	NS

Data are presented as the mean ± SD or the number (%) of patients.

Fig. 1. Event-free survival from MACE.

Kaplan-Meier analysis demonstrated a lower event-free survival rate in patients with a resistin level of >4.0 ng/mL than in those without ($p < 0.001$).

(95%CI=1.4-9.2, $p < 0.01$) with a resistin level of >4.0 ng/mL (Table 5).

Discussion

The present study investigated the associations of pre-procedural serum resistin levels with cardiovascular events and restenosis in 140 patients with CAD undergoing elective PCI; however, between patients with and without restenosis, pre-procedural serum resistin levels did not differ. During the 3-year follow-up, MACE occurred in 24 patients. Compared

Table 5. Factors associated with MACE (Multivariate Cox proportional hazard analysis in 140 study patients)

Variables	Hazard ratio (95%CI)	<i>p</i> value
Age (per 10-year increase)	2.1 (1.2-3.6)	< 0.02
Resistin level (>4.0 ng/mL)	3.6 (1.4-9.2)	< 0.01

Dependent variable was MACE. This analysis included age, gender, hypertension, diabetes, current smoking, number of stenotic coronary vessels, stent, statin, and hsCRP (>1.0 mg/L) and resistin (>4.0 ng/mL) levels.

with patients without MACE, those with MACE had higher resistin and hsCRP levels. Resistin levels correlated with hsCRP levels; however, in multivariate analysis, resistin levels were found to be independently associated with MACE.

Restenosis remains an important clinical problem after PCI. Among clinical risk factors, smoking is known to be a predictor of restenosis. In the present study, as shown in previous studies^{14, 15}, current smoking was found to be inversely associated with restenosis. Restenosis after angioplasty is caused by both negative arterial remodeling and neointimal proliferation, whereas in-stent restenosis is caused mainly by neointimal proliferation^{16, 17}. *In vitro*, resistin was reported to promote human smooth muscle cell proliferation⁸; therefore, resistin may play a role in the development of restenosis associated with neointimal proliferation. Recently, On *et al.*¹⁸ reported resistin levels to be higher in 35 diabetic patients who developed restenosis than in 35 diabetic patients who did not¹⁸; however, no correlation was found between

resistin levels and the severity of restenosis. In our study, only 33% of study patients had diabetes; however, pre-procedural serum resistin levels did not differ between patients with and without restenosis. Our results suggest that resistin does not play an important role in the development of restenosis. Of note was that resistin levels were high in patients who developed MACE and were an independent predictor of MACE but not restenosis.

Prospective data showing the association between resistin levels and cardiovascular events are still scarce. Recently, Weikert *et al.*¹⁹⁾ reported resistin levels and the risk of myocardial infarction and stroke in 26490 middle-aged subjects. This cohort study showed high resistin levels to be associated with an increased risk of myocardial infarction. Regarding patients with CAD, the AtheroGene study²⁰⁾ measured resistin levels in 1922 patients with CAD (1153 stable angina, 380 unstable angina, and 389 myocardial infarction). This study reported high resistin levels to be associated with cardiovascular death, but only 20% and 15% of study patients had planned to have CABG and PCI after angiography, respectively²¹⁾. In contrast, Hoeffle *et al.*²²⁾ reported no association between resistin levels and cardiovascular events in 547 patients undergoing coronary angiography; however, of the 547 patients, only 330 had CAD, some of whom had PCI or CABG after angiography. Therapeutic variables, such as PCI and CABG, were not considered in their analysis. In our study, blood samples were taken on the morning of the day of PCI, and all patients underwent elective PCI after blood sampling. As a result, serum resistin levels were significantly higher in patients with MACE than in those without, and high resistin levels were found to be independently associated with MACE in patients with CAD undergoing elective PCI.

Resistin has structural similarities to the proteins involved in inflammatory processes, especially FIZZ3²³⁾. In humans, resistin is secreted mainly by inflammatory cells, such as monocytes, and resistin expression was shown to be markedly increased by proinflammatory cytokines^{4, 5)}. As shown in previous studies^{11, 22)}, resistin levels correlated with hsCRP levels ($r=0.31$), but resistin levels did not correlate with any parameters of insulin resistance, such as fasting insulin levels or HOMA-IR. These findings suggest that resistin is therefore more likely to be related to inflammation than insulin resistance. Regarding plasma levels of hsCRP, a few studies^{24, 25)} have reported high pre-procedural hsCRP levels to be associated with the development of restenosis, whereas many other studies²⁶⁻²⁸⁾ have not. In contrast, many studies²⁴⁻²⁸⁾ have shown that hsCRP levels to predict cardiovascular

events in patients undergoing PCI. In our study, resistin or hsCRP levels were not high in patients with restenosis, but both resistin and hsCRP levels were high in patients with MACE. Serum resistin levels were found to be an independent predictor of MACE, while hsCRP levels were not. Our findings suggest that serum resistin levels may be a better predictor of MACE than hsCRP levels. Resistin levels are worth further evaluation of their predictive value for MACE in patients with CAD undergoing elective PCI.

Our study had several limitations. One of the major limitations was the relatively small number of study patients (140 patients), of whom only 97 (69%) had a bare metal stent. Any patients with drug-eluting stent implantation were excluded from our study. Therefore, our study should be considered preliminary, and a further study investigating the prognostic value of resistin levels on cardiovascular events in a larger number of patients with stent implantation, especially with a drug-eluting stent, is needed. In addition, only 94 (67%) patients underwent 6-month follow-up angiography. Regarding the association between serum resistin levels and angiographic restenosis, a further study with follow-up angiography in a larger number of patients is needed. Finally, only 15 patients (11%) had rest unstable angina before PCI. To elucidate the prognostic significance of resistin levels in patients with acute coronary syndromes, a further study is needed.

In conclusion, resistin appears to be related to inflammation. Pre-procedural serum resistin levels were found to be independently associated with further cardiovascular events in patients with CAD undergoing elective PCI, suggesting a potential role of resistin in the progression of atherosclerotic disease; however, our study could not show pre-procedural resistin levels to be a factor associated with angiographic restenosis.

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