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# High Serum Levels of Resistin is Associated With Acute Cerebral Infarction

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**Background:** The inflammatory process is involved in the pathogenesis of atherosclerosis and brain tissue injury following cerebral ischemia. Human resistin is a member of small cysteine-rich secreted proteins and has been implicated in inflammatory responses. This study investigated the association of serum resistin level with acute cerebral infarction (ACI). We also investigated its association with the short-term functional outcome.

**Methods:** This study included 106 patients with ACI and 106 age-matched and sex-matched healthy control subjects. Serum resistin level was assessed by using enzyme-linked immunosorbent sandwich assay. The association of serum resistin levels with ACI was analyzed by logistic regression analysis.

**Results:** The serum resistin level was significantly higher in patients with ACI than the control group [median (interquartile range), 35.7 ng/mL (13.0 to 70.5) ng/mL vs. 10.5 ng/ml (15.4 to 16.6), $P < 0.001$]. Logistic regression analysis showed that serum resistin level was associated with an ACI (odds ratio = 1.055, 95% confidence interval: 1.035-1.074, $P < 0.001$). Among stroke subtypes, the serum resistin level was higher in the patients with large artery atherosclerosis than those with other subtypes ($P = 0.013$). High resistin levels were also significantly associated with unfavorable functional outcome at discharge (odds ratio = 1.043, 95% confidence interval: 1.024-1.063, $P < 0.001$).

**Conclusions:** This study suggests the potential association of resistin with stroke and cerebral atherosclerosis. Increased serum resistin levels were also associated with early unfavorable neurological outcome.

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Ischemic stroke is a leading cause of disability and death.[1] Although different mechanisms are involved in the pathogenesis of stroke, accumulating evidence shows that inflammation is implicated in several aspects of acute ischemic stroke.[2] The inflammatory process is involved in the pathogenesis of atherosclerosis and brain tissue injury following cerebral ischemia.[3,4]

Resistin is a 114-amino acid polypeptide (12.5 kDa) hormone which belongs to a new gene family of small cysteine-rich secreted proteins.[5] Resistin is abundantly expressed in monocytes and macrophages in human. Resistin promotes endothelial cell activation and smooth muscle cell proliferation.[6–8] Serum resistin levels have a positive relation with plasma inflammatory biomarkers such as interleukin-6, soluble tumor necrosis factor-α receptor 2, and adhesion molecules.[9,10] Resistin also increases the expressions of various proinflammatory factors, including monocyte chemoattractant protein-1, endothelin-1, and matrix metalloproteinases, as well as adhesion molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and P-selectin.[11,12] Resistin increases the proliferation and migration of the vascular smooth muscle cells and human endothelial cells. Consequently, resistin increases endothelial permeability, which promotes endothelial cell, monocyte adhesion and infiltration.[13,14] Plasma resistin associated with inflammatory reaction of patients with type 2 diabetes mellitus, coronary atherosclerosis, chronic kidney disease, rheumatoid arthritis, acute pancreatitis and disease severity in patients with severe sepsis.[13–16] These findings suggest that resistin may have a potential role in the pathogenesis of atherosclerosis and cerebral ischemic injury. However, the inflammatory role of resistin in acute stroke remains unknown.

The aim of the present study was to investigate the relationship between the serum resistin level and acute cerebral infarction (ACI). This study also investigated the association of serum resistin with early functional outcome after stroke.

## METHODS

### Study Population

The study group consisted of patients with ACI who had been admitted within 48 hours after symptom onset to the Neurology Department from July 2007 to December 2011. This study included 106 consecutive patients (the patient group) whose informed consent was obtained. The control group consisted of 106 age-matched and sex-matched neurologically healthy subjects without any recent stroke history or any other thrombotic events which were recruited

from the outpatient clinic of our hospital for a scheduled health examination We assessed the previous history of stroke, cardiac diseases (such as atrial fibrillation, myocardial infarction, and valvular heart disease), hypertension, diabetes mellitus, and smoking in all subjects. Hypertension was diagnosed when a patient had a systolic blood pressure $\geq$ 140 mm Hg, a diastolic blood pressure $\geq$ 90 mm Hg, or was receiving antihypertensive treatment. Diabetes was diagnosed when a patient had a fasting plasma glucose level $\geq$ 7.0 mmol/L, hemoglobin A1C $\geq$ 6.5%, or had been receiving oral hypoglycemic agents or insulin.[17] We also determined serum levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. Body mass index was also determined. Hyperlipidemia was diagnosed as total cholesterol level $>$ 6.21 mmol/L, low-density lipoprotein cholesterol $>$ 4.14 mmol/L, or use of lipid-lowering medication after the diagnosis of hyperlipidemia. We did not include patients with severe hepatic dysfunctions (alanine aminotransferase or aspartate aminotransferase $>$ 2 times higher than the upper limit of normal value), renal dysfunction (serum creatinine $>$ 141.4 μmol/L), recent infection history, malignancy, previous history of peripheral vascular occlusive disease, autoimmune disease, or any other neurological disorders.

All patients with ACI underwent brain magnetic resonance imaging and angiographic studies (magnetic resonance angiography, or computerized tomography angiography, or conventional cerebral angiography). The severity of initial neurological deficits was assessed using the National Institutes of Health Stroke Scale (NIHSS). Functional neurological outcome was assessed by using modified-Rankin scale (mRS) at discharge. Unfavorable outcome was defined as mRS score $>$ 2 at discharge. Etiologic subtypes of stroke were determined according to the Trial of ORG 10172 in Acute Stroke Treatment classification system.[18] The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional human research ethical committee (IRB approval no. 2011-050). Informed consent was obtained from all subjects.

## Data Collection and Laboratory Examinations

All blood samples were obtained before initiating treatment (with an anticoagulant and/or an antiplatelet agent). Serum specimens were centrifuged, frozen within 2 hours of collection, and stored at –80°C until they were analyzed. Serum resistin levels were measured by using a commercially available enzyme-linked immunosorbent sandwich assay kit (Invitrogen, Camarillo, CA, USA). This kit used an affinity-purified polyclonal antihuman resistin antibody for coating. The same antibody was coupled to horseradish peroxidase for detection, according to the manufacturer's instructions. The lower detection limit of this assay was 100 pg/mL. The serum level of erythrocyte sedimentation rate and C-reactive protein (CRP) were also measured by standard laboratory method.

## Statistical Analysis

Statistical analysis was performed using SPSS (version 23.0; IBM SPSS Statistics, Armonk, NY, USA). Logistic regression analysis was used to determine the relationship between risk factors and ACI. After univariate analyses, odds ratio with 95% confidence interval (CI) were calculated using multivariate logistic regression. The goodness of fit of this model was assessed using Hosmer and Lemeshow $\chi^2$ statistics. The association of the serum resistin, erythrocyte sedimentation rate (ESR), and CRP level with stroke subtypes was assessed using the Kruskal-Wallis test with Bonferroni post hoc. The Student $t$ test or the Mann-Whitney $U$ test was used to compare the continuous variables between the patient group and the control group. The $\chi^2$ or the Fisher exact test was used to compare the categorical variables. Values were expressed as mean ± SD, median [interquartile range (IQR)], or number (percentage), as appropriate. Bivariate correlation between serum resistin levels and other parameters were compared using the Pearson correlation test. The receiver operating characteristic (ROC) curve analysis was performed to evaluate the prognostic potential of serum resistin for ACI. All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

# RESULTS

When compared with the control group, the patient group more frequently had systolic blood pressures, diastolic blood pressures, hypertension, diabetes mellitus, smoking, atrial fibrillation, or previous history of stroke (Table 1).

The median serum resistin level was significantly higher in the patient group than in the control group [35.7 (IQR: 13.0 to 70.5) ng/mL vs. 10.0 (IQR: 5.4 to 16.5) ng/mL; $P < 0.001$]. Univariate and multivariable analyses showed that the patient group had significantly higher systolic blood pressures and more frequently had a history of hypertension, smoking, or atrial fibrillation. After adjusting these confounding factors, the serum resistin level was significantly higher in the patient group than the control group ($P < 0.001$) (Table 2). The Hosmer and Lemeshow goodness of fit test supports that the model statistically fitted ($P > 0.05$).

We compared the serum resistin level according to the stroke subtypes. The serum resistin level was different among the stroke subtypes ($P = 0.036$), and it was highest in the subtype of large artery atherosclerosis (n = 31; median 55.52 ng/mL, IQR: 20.64 to 76.16). Bonferroni multiple comparison tests showed that the serum resistin level was significantly higher in large artery atherosclerosis than that in small vessel disease or

**TABLE 1.** Demographic and Clinical Characteristics

| | Patient (n = 106) | Control (n = 106) | *P* |
|---|---|---|---|
| Age, y | 68.0 ± 11.0 | 67.9 ± 10.9 | 0.965 |
| Sex, men | 52 (49.1) | 52 (49.1) | 1 |
| Systolic blood pressures, mm Hg | 148.4 ± 24.0 | 135.3 ± 23.3 | < 0.001 |
| Diastolic blood pressures, mm Hg | 81.4 ± 18.1 | 75.5 ± 14.7 | 0.010 |
| Height, m | 1.60 ± 0.09 | 1.61 ± 0.09 | 0.310 |
| Weight, kg | 60.7 ± 10.0 | 62.8 ± 10.8 | 0.136 |
| Body mass index, kg/m$^2$ | 23.8 ± 3.5 | 24.3 ± 3.4 | 0.277 |
| Hypertension | 57 (53.8) | 23 (21.7) | < 0.001 |
| Diabetes mellitus | 32 (30.2) | 11 (10.4) | 0.001 |
| Smoking | 36 (34.0) | 21 (19.8) | 0.030 |
| Cardiovascular disease* | 19 (17.9) | 10 (9.4) | 0.109 |
| Hyperlipidemia | 38 (35.8) | 32 (30.2) | 0.465 |
| Atrial fibrillation | 26 (24.5) | 8 (7.5) | 0.001 |
| Previous stroke | 27 (25.5) | 0 (0) | < 0.001 |
| Total cholesterol, mmol/L | 4.97 ± 1.15 | 4.92 ± 1.01 | 0.777 |
| Triglyceride, mmol/L | 1.54 ± 0.25 | 1.46 ± 0.20 | 0.010 |
| HDL-cholesterol, mmol/L | 1.15 ± 0.28 | 1.24 ± 0.40 | 0.078 |
| LDL-cholesterol, mmol/L | 3.11 ± 1.10 | 3.02 ± 1.03 | 0.543 |
| Resistin, ng/mL | 35.7 [13.0-70.5] | 10.0 [5.4-16.5] | < 0.001 |

Data are expressed as mean ± SD, number (%), or median [interquartile range].

*Cardiovascular disease includes coronary heart disease, heart failure, or peripheral arterial disease.

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

**TABLE 2.** Univariate and Multivariate Analysis of Risk Factors for Acute Cerebral Infarction

| | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | ***P*** | **OR** | **95% CI** | ***P*** |
| Systolic blood pressure | 1.024 | 1.011-1.037 | < 0.001 | 1.024 | 1.005-1.042 | 0.011 |
| Diastolic blood pressure | 1.023 | 1.005-1.041 | 0.012 | 1.010 | 0.982-1.037 | 0.495 |
| Height | 0.985 | 0.956-1.014 | 0.308 | | | |
| Weight | 0.980 | 0.955-1.006 | 0.136 | | | |
| Body mass index | 0.958 | 0.885-1.035 | 0.277 | | | |
| Hypertension | 4.198 | 2.306-7.643 | < 0.001 | 3.024 | 1.412-6.475 | 0.004 |
| Diabetes mellitus | 3.735 | 1.765-7.902 | 0.001 | 2.244 | 0.859-5.858 | 0.099 |
| Smoking | 2.082 | 1.115-3.886 | 0.021 | 2.484 | 1.080-5.716 | 0.032 |
| Cardiovascular disease* | 2.097 | 0.924-4.755 | 0.076 | | | |
| Hyperlipidemia | 1.292 | 0.728-2.294 | 0.381 | | | |
| Atrial fibrillation | 3.981 | 1.709-9.274 | 0.001 | 3.525 | 1.232-10.086 | 0.019 |
| Total cholesterol | 1.037 | 0.807-1.333 | 0.776 | | | |
| Triglycerides | 3.287 | 0.911-11.860 | 0.069 | | | |
| HDL-cholesterol | 0.490 | 0.221-1.087 | 0.079 | | | |
| LDL-cholesterol | 1.083 | 0.839-1.396 | 0.541 | | | |
| Resistin | 1.056 | 1.038-1.075 | < 0.001 | 1.060 | 1.040-1.081 | < 0.001 |

*Cardiovascular disease includes coronary heart disease, heart failure, or peripheral arterial disease.
CI indicates confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio.

unknown/undetermined causes (Table 3). No statistically significant difference in other inflammatory markers (ESR, CRP) was found among the 4 subtypes.

There was a trend towards to a higher level of serum resistin in patients with more severe neurological deficits (as demonstrated by higher NIHSS score). However, it was not significant ($r = 0.119$, $P = 0.223$).

An unfavorable functional outcome with mRS score $> 2$ at discharge was found in 44 patients (41.5%). In univariate and multivariable analyses, high resistin levels were independently associated with unfavorable functional outcome (odds ratio: 1.051, 95% CI: 1.030-1.073, $P < 0.001$) (Table 4). A ROC curve was generated for sensitivity and specificity, and the respective areas under the curve were used to investigate the prognostic value of serum resistin. ROC analysis showed that the cut-off value of serum resistin for predicting unfavorable outcome was 43.2 ng/mL (areas under the curve: 0.799, 95% CI: 0.717-0.881; $P < 0.001$). The sensitivity and specificity of the serum resistin were 68.2% and 67.7% (Fig. 1).

## DISCUSSION

Many studies have shown that some inflammatory biomarkers such as CRP, interleukin-6, and fibrinogen may be associated with myocardial infarction, cardiovascular death, peripheral arterial disease, and stroke.[19–22] This study showed that serum resistin levels as possible inflammatory biomarker increased in patients with ACI when compared with control subjects. Previous studies in the general population or in patients with cardiovascular risk factors showed inconsistent findings in the role of resistin in predicting risks of acute myocardial infarction and stroke. An elevated serum resistin concentration was a risk factor for ischemic stroke, especially for the lacunar and the atherothrombotic stroke in the general Japanese population.[23] In contrast, in patients with type 2 diabetes, the resistin levels had no influence on the risk of cardiovascular diseases including stroke.[24] In another study, high plasma resistin levels were related with an increased risk of myocardial infarction but not with a risk of ischemic stroke.[25] In the recent multiethnic study of atherosclerosis, there was a strong, independent association between higher resistin levels and cardiovascular disease.[26] While previous studies, which assessed the resistin level in the stable clinical condition, showed inconsistent results on the relationship between serum resistin levels and future risk of stroke, our findings demonstrated an association between the serum resistin levels and ACI.

We also found that the serum resistin level was associated with the stroke subtype of large artery atherosclerosis. Initially, resistin was thought to be a signaling protein that links insulin resistance to obesity.[27] However, in humans, it has been suggested that there is no relation between resistin and obesity or insulin resistance, but that resistin is related with subclinical inflammation[28,29] and the development of atherosclerosis.[6–8] Resistin induced a monocyte-endothelial cell adhesion by increasing the intercellular adhesion molecule-1 and the

**TABLE 3.** Relationship Between Serum Resistin and Stroke Etiology

| | Stroke Subtype | | | | |
|---|---|---|---|---|---|
| | **Large Artery Atherosclerosis** | **Cardioembolism** | **Small Vessel Disease** | **Unknown/ Undetermined Causes** | ***P*** |
| Number of subjects, n (%) | 31 (29.2) | 30 (28.3) | 26 (24.5) | 19 (17.9) | |
| Serum resistin (ng/mL) | 55.52 (20.64-76.16) | 34.86 (15.29-67.95) | 21.64 (4.94-63.88) | 15.92 (6.08-68.32) | 0.036 |

Data are expressed as median (interquartile range).

 

**TABLE 4.** Univariate and Multivariate Analysis for Unfavorable Outcome

| | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | ***P*** | **OR** | **95% CI** | ***P*** |
| Age | 1.041 | 1.001-1.081 | 0.042 | 1.079 | 1.023-1.139 | 0.006 |
| Sex | 0.781 | 0.360-1.695 | 0.532 | | | |
| Systolic blood pressure | 0.990 | 0.974-1.007 | 0.241 | | | |
| Diastolic blood pressure | 0.981 | 0.959-1.005 | 0.121 | | | |
| Body mass index | 0.996 | 0.893-1.112 | 0.948 | | | |
| Hypertension | 2.348 | 1.056-5.221 | 0.036 | 2.482 | 0.863-7.141 | 0.092 |
| Diabetes mellitus | 0.788 | 0.336-1.844 | 0.582 | | | |
| Smoking | 0.848 | 0.374-1.927 | 0.695 | | | |
| Cardiovascular disease* | 1.337 | 0.493-3.625 | 0.568 | | | |
| Hyperlipidemia | 2.037 | 0.908-4.570 | 0.084 | | | |
| Atrial fibrillation | 3.708 | 1.461-9.411 | 0.006 | 2.403 | 0.666-8.672 | 0.180 |
| Previous stroke | 1.759 | 0.729-4.245 | 0.209 | | | |
| Admission NIHSS score | 1.241 | 1.077-1.431 | 0.003 | 1.221 | 1.021-1.460 | 0.029 |
| Stroke subtypes | | | | | | |
| Large artery atherosclerosis | REF | | | | | |
| Cardioembolism | 2.077 | 0.748-5.765 | 0.161 | | | |
| Small vessel disease | 0.733 | 0.249-2.154 | 0.572 | | | |
| Unknown/undetermined causes | 0.369 | 0.099-1.373 | 0.137 | | | |
| Total cholesterol | 1.356 | 0.957-1.920 | 0.086 | | | |
| Triglycerides | 2.086 | 0.362-12.036 | 0.411 | | | |
| HDL-cholesterol | 1.056 | 0.266-4.195 | 0.938 | | | |
| LDL-cholesterol | 1.349 | 0.939-1.937 | 0.105 | | | |
| Resistin | 1.037 | 1.022-1.053 | < 0.001 | 1.051 | 1.030-1.073 | < 0.001 |
| ESR | 1.017 | 0.993-1.041 | 0.170 | | | |
| CRP | 1.732 | 0.876-3.424 | 0.114 | | | |

*Cardiovascular disease includes coronary heart disease, heart failure, or peripheral arterial disease.

CI indicates confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rates; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

vascular cell adhesion molecule-1 expression in endothelial cells.[30,31] Resistin promoted lipid accumulation in human macrophages by upregulating the CD 36 cell surface expression. Resistin was suggested to act as a modulator for foam cell transformation from macrophages.[32] Inflammation plays an important role in the development of atherosclerosis.[4] Thus, these relations between resistin, inflammation, and atherosclerosis may reasonably explain the mechanism of the high serum resistin level in large artery atherosclerosis of our study group.

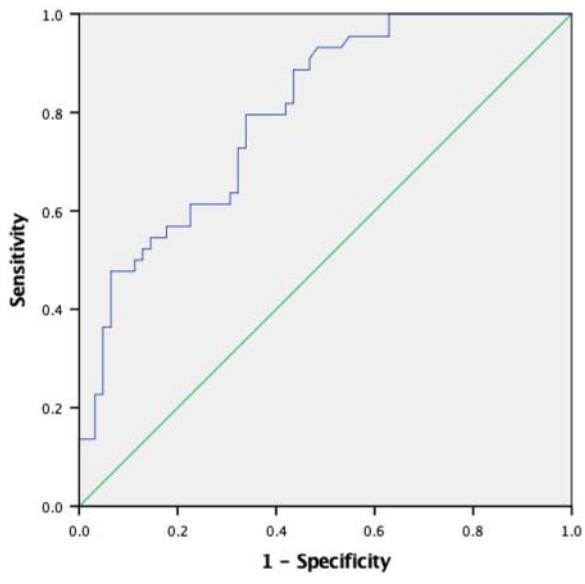


**FIGURE 1.** The receiver operating characteristic curve of serum resistin in distinguishing unfavorable outcome from favorable outcome.

In this study, patients with high serum resistin level had unfavorable functional outcomes. The exact mechanism by which serum resistin might influence stroke outcome is unknown. However, when considering that inflammation contributes to ischemic injury and resistin is associated with inflammation, resistin may be associated with ischemic injury. There are several studies that might explain the relationship between serum resistin level and functional outcome.[33,34] These studies suggested that serum resistin contributes to the development of atherosclerosis by upregulating cytokines and adhesion molecule expression on human endothelial cells. These excessive inflammatory responses in coronary and cerebral arteries may be associated to its unfavorable outcome, independently of other adverse predictors.[33]

This cross-sectional study had some limitations. First, all blood samples to measure serum resistin levels were obtained during the acute phase of cerebral infarction. Therefore, whether elevated serum resistin levels may be a risk factor or a consequence of ACI remains uncertain. Second, our study had a small sample size with single ethnicity. In this study, ESR and CRP levels did not have a statistically significant association with ACI, but their possibility of being related in studies involving a larger number of patients cannot be excluded. As the study of a larger population proceeds, whether the elevated serum resistin levels in this population is a pre-existing risk factor or simply reflects an acute inflammatory response will become clear. Third, control subjects were selected on the basis of their clinical history, without conducting any brain imaging

studies. Therefore, there might be patients with a silent cerebral infarction. In addition, angiography was not performed in the control group. A study including subjects with large artery atherosclerosis but without ACI might have been valuable for teasing out whether elevated resistin levels are simply related to large artery atherosclerosis. Finally, statins were not included in the analysis. Statins may affect the levels of acute phase reactants and atherosclerosis; hence further research is needed for investigation.

In conclusion, the present study showed the increased levels of resistin in patients with ACI, particularly in which with large artery atherosclerosis. The plasma level of serum resistin was also associated with short-term functional outcomes. These associations may be attributed to the role of resistin on vascular inflammation.



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