Influence of serum resistin on acute cerebral infarction

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Influence of serum resistin on acute cerebral infarction

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ABSTRACT

Influence of serum resistin on acute cerebral infarction

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Background

Human resistin, which is a member of small cysteine-rich secreted proteins, has been implicated in inflammatory responses in several inflammatory conditions, such as acute pancreatitis, ankylosing spondylitis, Kawasaki disease and atherosclerosis. However, the relation between the serum resistin level and ischemic stroke has not been clearly elucidated. The aim of this study is to assess the clinical role of serum resistin in patients with acute cerebral infarction.

Methods

A total of 106 patients with acute cerebral infarction and 70 age-matched healthy control subjects were included in this prospective study. Serum resistin levels were determined by enzyme-linked immunosorbent sandwich assay in the patient and control group.

Results

The serum resistin level was significantly higher in the patient group (37.6 ± 28.8 ng/ml) compared with the control group (19.2 ± 21.5; P <0.001). We also

found that, as the quartile level of serum resistin increased, each adjusted relative odds ratio (OR) for stroke event increased. The highest quartile level of serum resistin was significantly associated with the increased risk of acute cerebral infarction (OR=5.79; $P = 0.002$). When we assessed the relation between serum resistin and stroke subtypes classified as per the Trial of ORG 10172 in Acute Stroke Treatment Classification, the serum resistin level in the large artery atherscelrosis subtype increased significantly (49.2 ± 28.4 ng/ml; $P = 0.016$).

Conclusion

This study provides a more specific additional evidence of relation between the high serum resistin concentration and acute cerebral infarction, especially in the large artery atherosclerosis subtype. Further large-scale prospective studies are required to confirm the role of serum resistin in acute cerebral infarction.

Key words: serum resistin, acute cerebral infarction, stroke subtype

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I. INTRODUCTION

Ischemic stroke is a leading cause of severe disability and death.[1] In the majority of cases, stroke is believed to be a multifactorial disorder. Although different mechanisms are involved in the pathogenesis of stroke, increasing evidences show that inflammation is implicated in several aspects of acute ischemic stroke.[2] Inflammatory processes are involved in the pathogenesis of atherosclerosis and brain tissue injury following cerebral ischemia.[3,4]

Ischemic stroke begins with transient or permanent reduction in cerebral blood flow, which leads to energy failure, excitotoxicity and oxidative damage. As the result of these damages, secondary deleterious phenomena, such as microvascular injury, blood brain barrier dysfunction and inflammatory responses, occur, which may exacerbate the initial injury and can lead to permanent cerebral damage.[5]

Many studies have shown that some inflammatory biomarkers such as C-

reactive protein (CRP), interleukin 6, and fibrinogen may be associated with myocardial infarction, stroke, cardiovascular death, and peripheral arterial disease.[6-9]

Resistin is a 114-amino acid polypeptide (12.5 kDa) hormone that belongs to a new gene family of small cysteine-rich secreted proteins.[10] Resistin is abundantly expressed in monocytes and macrophages in human, and promotes endothelial cell activation and smooth muscle cell proliferation.[11-13] Serum resistin levels had a positive relation with plasma inflammatory biomarkers, such as interleukin (IL)-6, soluble tumor necrosis factor (TNF)- α receptor 2, or adhesion molecules.[14,15] These facts suggested that resistin may have a potential role in the pathogenesis of atherosclerosis.

The aim of the present study is to investigate the relation between the serum resistin level and acute cerebral infarction, taking various subtypes of cerebral infarction into account .

II. MATERIALS AND METHODS

1. Patient selection

The study group consisted of patients with acute cerebral infarction who had been admitted to the department of neurology, Konyang University Hospital, Daejeon, Korea from July, 2008 to Dec, 2010. All patients were examined by brain magnetic resonance imaging (MRI), including T2-weighted and diffusion-weighted sequences. We assessed the previous stroke history, cardiac diseases

(such as atrial fibrillation, myocardial infarction, and valvular heart disease), diabetes mellitus, hypertension, and smoking in all subjects. Serum total cholesterol, high-density lipoprotein cholesterol, and body mass index were also determined.

Exclusion criteria were severe hepatic dysfunctions (alanine aminotransferase or aspartate aminotransferase > 2 times as high as the upper limit of normal value) or renal dysfunction (serum creatinine > 1.6 mg/dL), recent infection history, malignancy, and previous history of neurologic disorders including peripheral vascular occlusive disease, autoimmune disease, or any other neurologic disorders.

2. Definition and diagnosis of acute cerebral infarction

Acute cerebral infarction was diagnosed on the basis of clinical symptoms and imaging evidence of computed tomography or MRI, and only confirmed cases were considered for analysis. The severity of neurologic deficits and the functional status of patients were assessed using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) by a certified vascular neurologist.[16,17] With all available clinical, laboratory and neuroimaging data, etiologic subtypes were determined according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.[18]

3. Control group selection

The control group consisted of 70 patients whose primary symptoms were headache and dizziness, without any recent stroke history or any other thrombotic events.

This study was approved by the human research ethical committee at College of Medicine, Konyang University, Daejeon, Korea. Informed consent was obtained from all subjects.

4. 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 and frozen within 2 hours of collection and stored at –80ºC until they were analyzed. Serum resistin levels were measured by the enzyme-linked immunosorbent sandwich assay (ELISA) kit commercially available (Invitrogen, Camarillo, CA, USA), which employed an affinity-purified polyclonal anti-human resistin antibody for coating and 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. Tests were performed in one laboratory by a single operator. The serum erythrocyte sedimentation rates (ESR), CRP, total cholesterol and high density lipoprotein (HDL) cholesterol were measured by conventional methods in our hospital laboratory.

5. Statistical analysis

We divided the subjects into quartiles according to their respective resistin level as follows: < 8.64, 8.73 to 17.60, 18.35 to 49.76 and ≥ 50.08 ng/ml. The role of serum resistin in stroke was assessed by comparing the control group with the patient group. Logistic regression analysis was used to determine the relation between risk factors and acute cerebral infarction. After univariate analyses, odds ratio (OR) with 95% confidence interval (CI) were calculated using multivariate logistic regression. In addition, we assessed the relation between the stroke subtype and the serum resistin level using one-way analysis of variance (ANOVA). Student's t-test was used to compare continuous variables between the patient group and the control group. Chi-square and Fisher's exact tests were used to compare categorical variables. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as numbers and percentages. Statistical analysis was performed using SPSS version 12.0 (Chicago, IL, USA). $P < 0.05$ was considered significant.

III. RESULTS

1. Subject demographics and clinical characteristics

The clinical characteristics, demographics and laboratory findings for the participants are shown in Table 1. When compared with the control group,

hypertension, diabetes mellitus, smoking and previous stroke were more common in the patient group. Besides, the serum resistin level was also higher in the patient group (37.6 ± 28.8 ng/ml) than the control group (19.2 ± 21.5 ng/ml; P <0.001).

Table 1. Subject demographics and clinical characteristics.

	Patient	**Control**	***P*-value**
Number of subjects (*n*)	106	70	
Age (years)	68.0±11.0	65.1±11.3	0.095
Sex (male/female)	52/54	29/41	0.320
Height (m)	1.60±0.09	1.61±0.09	0.362
Weight (kg)	60.7±10.0	63.2±11.2	0.119
BMI (kg/m^2)	23.8±3.5	24.2±2.8	0.378
Hypertension (%)	53.8	15.7	<0.001
DM (%)	30.2	7.1	<0.001
Smoking (%)	34.0	17.1	0.014
Cardiac disease (%)	17.9	8.6	0.082
Previous stroke (%)	25.5	0	<0.001
Cholesterol (mmol/L)	4.72±1.11	5.27±1.03	0.001
HDL Cholesterol (mmol/L)	1.15±0.28	1.18±0.60	0.733
Resistin (ng/ml)	37.6±28.8	19.2±21.5	<0.001

Data are expressed as mean ± SD. BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; Cardiac disease includes atrial fibrillation, myocardial infarction, and valvular heart disease.

2. Univariate analysis of risk factors

Univariate analysis showed that older age (> 65 years old), hypertension, diabetes mellitus, smoking, cardiac disease, total cholesterol and serum resistin level were significantly related with cerebral infarction (Table 2).

Table 2. Univariate analysis of risk factors for cerebral ischemic events.

	OR	95% CI	*P*-value
Sex (male)	1.36	0.74-2.50	0.321
Age (>65)	1.95	1.04-3.65	0.037
Hypertension	6.24	2.95–13.19	<0.001
DM	5.62	2.07-15.28	0.001
Smoking	2.49	1.19–5.21	0.016
Cardiac disease	2.33	0.88-6.16	0.088
BMI (>25)	0.65	0.34-1.22	0.18
Cholesterol (>6.47mmol/L)	0.43	0.23-0.81	0.009
HDL cholesterol (>1.16mmol/L)	0.78	0.43-1.43	0.425
Serum resistin (quartile, ng/ml)			
0-8.64			
8.73-17.60	1.90	0.82-4.43	0.137
18.35-49.76	2.79	1.18-6.64	0.02
50.08-123.67	4.91	1.95-12.4	0.001

CI, confidence interval; OR, odds ratio; DM, diabetes mellitus; BMI, body mass index; HDL, high-density lipoprotein; Cardiac disease includes atrial fibrillation, myocardial infarction, and valvular heart disease.

3. Logistic regression analysis

We have examined the possible interaction between the serum resistin level and stroke risk factors. Statistically, no significant first order interaction was observed between the resistin level and stroke risk factors. When we analyzed risk factors for acute cerebral infarction, we found that, as the quartile level of serum resistin increased, each adjusted relative OR also increased. The highest quartile of the serum resistin level was related with the significantly increased risk of acute cerebral infarction. Adjusted OR of the highest quartile of serum resistin was 5.79 for stroke event (95% CI, 1.92–17.52; $P = 0.002$), which was higher than adjusted ORs of other conventional risk factors for stroke (Table 3).

Table 3. Adjusted relative odds ratios of cerebral infarction related with various risk factors.

	OR	**95% CI**	***P*-value**
Age (>65)	2.38	1.11-5.11	0.025
Hypertension	3.8	1.65–8.77	0.002
DM	3.49	1.12-10.87	0.031
Smoking	2.55	1.05–6.17	0.039
Cardiac disease	2.04	0.64-6.56	0.231
Cholesterol (>6.47mmol/L)	0.49	0.23-1.04	0.063
Serum resistin (quartile, ng/ml)			
0-8.64			
8.73-17.60	1.78	0.64-4.97	0.274
18.35-49.76	2.8	1.02-7.73	0.046
50.08-123.67	5.79	1.92-17.52	0.002

CI, confidence interval; OR, odds ratio; DM, diabetes mellitus; Cardiac disease includes atrial fibrillation, myocardial infarction, and valvular heart disease.

4. Relation between serum resistin and stroke etiology

When we assessed the relation between the serum resistin level and stroke subtypes on the basis of the TOAST classification, significant differences were observed among the stroke subtypes (P = 0.016). The serum resistin level was highest in the subtype of large artery atherosclerosis, followed by cardioembolism and small vessel occlusion and unknown/undetermined stroke (Table 4). No statistically significant difference in other inflammatory markers (ESR, CRP) was found among the four subtypes (Table 4).

Table 4. Relationship between serum resistin level and stroke subtypes

	Stroke subtype				*P*-value
	Large artery stroke	**Cardioembolic stroke**	**Small vessel stroke**	**Unknown/undetermined stroke**	
Number of subjects (n)	37	17	29	23	
Serum resistin (ng/ml)	49.2±28.4	36.7±25.4	29.8±28.2	29.3±27.9	0.016
ESR (mm/h)	21.73±17.84	21.12±14.61	19.07±13.77	21.74±20.55	0.922
CRP (mg/dl)	1.08±1.97	1.15±2.22	0.72±1.01	1.33±3.28	0.781

Data are expressed as mean ± SD. ESR, erythrocyte sedimentation rates; CRP, C-reactive protein.

5. Relation between serum resistin and stroke severity

Although CRP increased with quartiles of resistin, it was not statistically significant ($P = 0.093$). There was a trend towards higher level of serum resistin in patients with more severe neurologic deficits (as demonstrated by higher NIHSS score), however it was not significant ($r = 0.17$, $P = 0.081$).

IV. DISCUSSION

In our study, serum resistin levels increased in patients with acute ischemic stroke. Initially, resistin was thought to be a signaling protein to provide a relation between obesity and insulin resistance.[19] However, in humans, it has been suggested that there is no relation between resistin and obesity or insulin resistance, and that resistin is more related with subclinical inflammation than insulin resistance.[20,21] Recently, resistin was shown to contribute to development of atherosclerosis.[11-13] Resistin induced monocyte-endothelial cell adhesion by increasing intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) expression in endothelial cells.[22,23] Another study showed that resistin promoted lipid accumulation in human macrophages by upregulating CD36 cell surface expression and might act as a modulator for macrophage to foam cell transformation.[24] However, the relation between serum resistin levels and ischemic stroke has not been clearly elucidated. Previous studies showed a controversial evidence of serum resistin in acute cerebral

ischemic events.[25-27] In a Hisayama study, the elevated serum resistin concentration was a risk factor for ischemic stroke, especially lacunar and atherothrombotic stroke in the general Japanese population.[27] In contrast, a 42-month prospective study of Korean patients with type 2 diabetes showed that resistin levels had no influence on the risk of cardiovascular diseases including stroke.[25] In another study, high plasma resistin levels were related with an increased risk of myocardial infarction but not with a risk of ischemic stroke.[26]

In the present study, we found that high serum resistin levels may be a factor related with the risk of ischemic stroke. Regarding stroke subtypes, our study demonstrated that serum resistin seemed to be related to large artery stroke. Inflammation is a major factor for development of atherosclerosis.[4] Thus, these relations between inflammation and atherosclerosis may reasonably explain the mechanism of the high serum resistin level as a related factor to large artery stroke.

Notably, in our study, there was a trend towards higher serum resistin levels as the more severe neurologic deficit although it was not statistically significant. The higher serum resistin level in the more severe stroke may be explained by the higher resistin level in large artery atherosclerosis. Usually, large artery atherosclerosis produces multiple and large ischemic lesions which may cause more severe stroke.[28]

This study has several limitations. First, all subjects were Koreans, which may restrict application of the study results to Korean patients. Second, all blood

sampling for serum resistin measurements was performed during the acute stage of a cerebral ischemic event. We did not measure the serum resistin level during the stable period after cerebral infarction. Therefore, it is not clear whether the high serum resisitn level is a risk factor or a consequence of acute cerebral infarction. To resolve this question, serial measurements of the serum resitin level would be helpful. Third, our study had a small sample size.

V. CONCLUSION

The present findings provides a more specific additional evidence of relation between the high serum resistin level and acute cerebral ischemia, especially in the large artery atherosclerosis subtype.

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ABSTRACT(IN KOREAN)

혈청 레지스틴이 급성 뇌경색에 미치는 영향

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배경

시스테인이 풍부한 분비 단백질의 일종인 사람 레지스틴은 급성 췌장염, 강직성 척추염, 가와사키 병 및 동맥경화증과 같은 여러 염증성 조건들에서의 염증 반응과 연관성이 있다고 보고되어졌다. 그러나, 혈청 레지스틴 수치와 허혈성 뇌졸중과의 관계는 아직까지 명확히 밝혀지지 않았다. 본 연구의 목적은 급성 허혈성 뇌졸중에서의 혈청 레지스틴 수치의 임상적 의미를 평가하는 것이다.

방법

총 106 명의 급성 허혈성 뇌졸중 환자와 70 명의 연령을 짝지은 건강한 대조군이 본 전향연구에 포함되었다. 혈청 레지스틴 수치는 환자군과 대조군 모두에서 효소 면역 측정법에 의하여 측정되었다.

결과

혈청 레지스틴 수치는 환자군에서 (37.6 ± 28.8 ng/ml) 대조군보다

(19.2 ± 21.5; P <0.001) 의미있게 높았다. 또한 혈청 레지스틴 수치의 사분위가 올라갈수록 각각의 조정 상대적 대응비 또한 함께 상승하였다. 가장 높은 사분위의 혈청 레지스틴 수치는 급성 뇌경색의 위험도를 의미있게 상승시켰다 (OR, 5.79; P = 0.002). 혈청 레지스틴 수치와 Trial of ORG 10172 in Acute Stroke Treatment 뇌졸중 분류에 따른 뇌졸중 아형과의 관계를 살펴보았을 때, 혈청 레지스틴 수치는 대동맥동맥경화성 뇌졸중에서 의미 있게 높았다 (49.2 ± 28.4 ng/ml; P = 0.016).

고찰

본 연구에서 고농도의 혈청 레지스틴과 급성 허혈성 뇌졸중과의 연관성을 볼 수 있다. 특히 대동맥동맥경화성 뇌졸중과 혈청 레지스틴과의 관계를 본 연구에서 볼 수 있었다. 본 연구에서 언급된 혈청 레지스틴의 급성 허혈성 뇌졸중에서의 역할에 대하여 확증하기 위해서는 향후 보다 대규모의 전향적 연구가 필요할 것이다.

핵심되는 말 : 혈청 레지스틴, 급성 허혈성 뇌졸중, 뇌졸중 아형

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