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Original Article

Omentin-1 is Associated with Carotid Plaque Instability among Ischemic Stroke Patients

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***Aims*: Omentin-1 was proved to be associated with ischemic stroke clinical functional outcome. It also predicted carotid atherosclerosis among metabolic syndrome subjects and type 2 diabetes patients. Our aim was to examine the association of omentin-1 levels with carotid plaque instability and stenosis degree among ischemic stroke patients.**

***Methods*: A total of 173 acute ischemic stroke patients were included in this study. Serum omentin-1 levels were assayed. Carotid ultrasound examinations were performed to evaluate the carotid plaque instability and stenosis degree. Multivariable logistic analyses were used to examine the association of serum omentin-1 levels with carotid plaque instability and stenosis degree.**

***Results*: Ischemic stroke patients with unstable carotid plaque had significantly lower levels of serum omentin-1 than patients with stable plaque (53 [40.2–64.1] vs 61.8 [52.4–77.2] ng/ml, $P<0.01$). Subjects in the highest tertile of serum omentin-1 levels had a 0.31-fold risk of having unstable plaque compared with those in the lowest tertile ($P<0.05$), and its trend test was significant (P for trend = 0.03). The integrated discrimination improvement was significantly improved in predicting carotid plaque instability when omentin-1 data was added to the multivariable logistic regression model. No significant association was detected between omentin-1 and moderate–severe carotid stenosis or occlusion.**

***Conclusions*: Among ischemic stroke patients, higher omentin-1 levels were inversely associated with carotid plaque instability, but not associated with moderate–severe carotid stenosis or occlusion. Omentin-1 may represent a biomarker for predicting carotid plaque instability of acute ischemic stroke patients.**

Key words: Omentin-1, Carotid plaque instability, Carotid stenosis, Ischemic stroke

Introduction

Stroke is the second-most common cause of death and a leading cause of long-term disability worldwide. Ischemic stroke is by far the most common type of stroke, accounting for approximately 70%–90% of all stroke cases[1]. Ischemic stroke is usually caused by acute thrombosis, which is triggered by unstable atherosclerotic plaque or vascular stenosis. The identification of novel biomarkers that can predict carotid atherosclerosis among ischemic stroke patients has clinical significance in primary and secondary prevention of ischemic stroke.

Omentin is primarily expressed in visceral adipose stromal vascular cells but is also expressed in lung, heart, placental, and ovarian tissues[2, 3]. It has two highly homologous isoforms, namely, omentin-1 and omentin-2. Omentin-1 is the major circulating isoform in human plasma. Some population studies reported that omentin-1 was significantly associated with carotid atherosclerosis among metabolic syndrome subjects and type 2 diabetes patients[4, 5]. Our previous study has also demonstrated that higher omentin-1 levels at baseline were inversely associated

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with poor functional outcome among ischemic stroke patients[6]. To date, no study has specifically evaluated the association between omentin-1 levels and carotid atherosclerosis among ischemic stroke patients.

Aim

We thus aimed to investigate the relationship between serum omentin-1 levels with carotid plaque instability and stenosis degree among acute ischemic stroke patients in China.

Methods

Study Participants

There were 173 consecutive patients with acute ischemic stroke in this study. Participants who did not have any pre-morbid handicap were admitted to the Department of Neurology of the Affiliated Hospital of Nantong University between October 2015 and June 2016. The definition of acute ischemic stroke complied with the World Health Organization criteria[7]. The inclusion criteria were (1) pre-morbid modified Ranking Scale ≤ 2, (2) symptom onset within 7 days, (3) ischemic stroke confirmed by computed tomography or magnetic resonance imaging of the brain, and (4) carotid ultrasound examinations performed during the hospitalization. The exclusion criteria were (1) malignancies, (2) intracerebral hemorrhage, (3) transient ischemic attack, (4) renal or hepatic disease, and (5) ischemic stroke without carotid plaque. Our study also enrolled 172 healthy volunteers who had no history of cardiovascular or cerebrovascular diseases as the control group. This study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board of the Affiliated Hospital of Nantong University. Written informed consent was obtained from all study participants or their immediate family members.

Baseline Data Collection

Demographic characteristics, lifestyles parameters, and medical histories were collected upon admission via in-person interviews with the patients or their family members. Cigarette smoking was defined as having smoked ≥ 1 cigarette per day for ≥ 1 year. Drinking was defined as having consumed any type of alcoholic beverage at least once per week for the past year. Several diseases were defined below: (1) hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg being reported in the patient's medical record or any patient receiving antihypertensive treatment; (2) diabetes mellitus was defined as a fasting glucose level ≥ 7.0 mmol/L and/or postprandial blood glucose ≥ 11.1 mmol/L being reported in the patient's medical record or the patient receiving insulin or oral hypoglycemic medication; (3) the confirmation of previous stroke was based on the sudden onset of nonconvulsive and focal neurological deficits persisting for >24 h being recorded in the patient's medical history; (4) previous coronary artery disease was defined as a condition that reduces blood flow through the coronary arteries to the heart and typically results in chest pain or heart damage recorded in the patient's medical history; and (5) previous atrial fibrillation was defined as an abnormal heart rhythm characterized by rapid and irregular heartbeat being recorded in the patient's medical history. Pre-stroke antithrombotics, antihypertensive, and statin treatment were also recorded. Height and weight were recorded upon admission, and BMI was subsequently calculated. The National Institutes of Health Stroke Scale was used to evaluate stroke severity at admission[8]. According to the symptoms and imaging data of the patients, the ischemic stroke subtype was classified as large artery atherosclerosis, cardiac embolism, small artery occlusion lacunae, acute stroke of other demonstrated etiology, or stroke of other undemonstrated etiology[9]. Three blood pressure measurements were obtained at baseline with the participant in the supine position using a standard mercury sphygmomanometer[10]. A modified hexokinase enzymatic method was employed to test plasma glucose levels. Total cholesterol, high density lipoprotein cholesterol, and triglycerides were analyzed enzymatically using commercial reagents. Low density lipoprotein cholesterol levels were calculated using the Friedewald equation.

Serum Omentin-1 Assay

Blood samples were collected at 6:00 am within 24 h of hospital admission after at least 8 h of fasting. After at least 30 min of clotting, the serum was separated, and all specimens were stored at −80℃ until testing. After all participants were included in this study, omentin-1 was measured unifiedly at November 2016. The serum omentin-1 assay was performed using a commercial enzyme-linked immunosorbent assay kit (catalog number: CK-I1513H, IBL International, Hamburg, Germany) according to the manufacturer's instructions. A standard curve was plotted, from which the omentin-1 concentrations of unknown samples were determined. The laboratory technicians who performed these measurements were blinded to the baseline characteristics and carotid ultrasound examination results of the study participants. Omentin-1 is known to remain stable in blood samples frozen at −80℃ after several cycles of freezing

and thawing[11].

Carotid Ultrasound Examination

All patients underwent carotid ultrasonic examination using a Philips color Doppler ultrasonic diagnostic apparatus (IU elite, Royal Philips, Netherlands) by experienced physicians and technicians who were blind to the clinical data including omentin-1 levels of all patients. The carotid ultrasound examination results were also reviewed by these experienced physicians and technicians. Discrepancies between their evaluations were resolved by consensus. The frequency of peripheral vascular ultrasound was 1–9 Hz. Vertical scanning along the lateral edge of the sternocleidomastoid muscle followed by transverse scanning was performed with the subjects in the supine position with their heads turned to the opposite side of the examined region. The examination protocol involved scanning of the common carotid arteries, the carotid bifurcations, and the origin (first 1.5 cm) of the internal carotid arteries and external carotid arteries. Carotid plaque was demonstrated as a thickness of 1.5 mm from the intima–lumen interface to the media adventitia interface. In this study, unstable carotid plaques were defined based on: (1) plaques with incomplete fibrous cap or ulcerated plaques, according to the plaque morphology—fibrous cap is a layer of fibrous connective tissue, which is thicker and less cellular than the normal intima; the minimum depth of "ulcerated plaques" is at least 2 mm depth—and (2) plaques with low-level or heterogeneous echoes, according to the plaque echodensity. The degree of stenosis was assessed with the velocity criteria. Carotid artery peak systolic velocity and presence of plaque on color Doppler images are primarily used in diagnosis and grading of carotid stenosis[12]. The degree ≥ 50% was defined as moderate–severe stenosis or occlusion. The degree < 50% was defined as none or mild stenosis.

Statistical Analysis

Because of its skewed distribution, the serum concentration of omentin-1 was presented as a median together with a 25^{th}-to-75^{th}-percentile range and compared using the Wilcoxon signed-rank test. Between the stable carotid plaque group and the unstable carotid plaque group as well as the none or mild stenosis group and the moderate–severe stenosis or occlusion group, baseline information was compared using one-way ANOVA, the Wilcoxon signed-rank test or the chi-squared test, as appropriate. The rates of unstable carotid plaque and moderate–severe carotid stenosis or occlusion among omentin-1 tertiles were calculated and compared by the chi-squared test.

All participants were classified according to tertiles of serum omentin-1 levels (< 47, 47–61.1, and ≥ 61.1 ng/ml). Multivariable logistic regression analyses were used to estimate the risk of unstable carotid plaque and moderate–severe stenosis or occlusion associated with omentin-1 levels. Odds ratios (ORs) and 95% confidence intervals (CIs) for higher tertiles compared to the lowest tertile and for per-unit increase of log-transformed serum omentin-1 levels after adjustment for possible confounders ($P < 0.1$ in the univariate analysis) were calculated. A linear trend test was performed by entering omentin-1 tertiles as continuous parameters in the model. The integrated discrimination improvement (IDI) was calculated to evaluate the predictive value of adding omentin-1 to conventional risk factors for predicting unstable carotid plaque and moderate–severe carotid stenosis or occlusion among ischemic stroke patients[13]. All statistical tests were two-tailed and were considered significant if the *P*-values were less than 0.05. Statistical analyses were conducted using SAS (version 9.3; SAS Institute, Cary, NC, USA) and R software (version 3.0; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Ischemic stroke patients had significantly lower levels of serum omentin-1 than healthy controls (55.9 [42.1–65.2] vs 122.2 [112.1–132.0] ng/ml, $P < 0.01$). As shown in **Table 1**, ischemic stroke patients with unstable carotid plaques were more likely to have higher blood glucose levels, history of hypertension and diabetes, and pre-stroke antihypertensive treatment, but less likely to have cardioembolic subtype and a history of coronary artery disease. In addition, ischemic stroke patients with moderate–severe stenosis or occlusion tended to have large vessel atherosclerosis subtype and non-cardioembolic subtype, and to have lower diastolic blood pressure levels.

In **Fig. 1**, ischemic stroke patients with unstable carotid plaques had significantly lower levels of serum omentin-1 than patients with stable carotid plaques (53 [40.2–64.1] vs 61.8 [52.4–77.2] ng/ml, $P < 0.01$). However, there was no significant difference in omentin-1 levels between ischemic patients with none or mild carotid stenosis and those with moderate–severe stenosis or occlusion (54.9 [42–64.8] vs 58.1 [45.8–67.5] ng/ml, $P = 0.63$]. In **Fig. 2**, the rates of unstable carotid plaque for each omentin-1 tertile were 87.9%, 79.7%, and 66.1%, respectively ($P = 0.02$). In contrast, there was no significant difference in the rates of moderate–severe stenosis or occlusion among omentin-1 tertiles as the rates were 13.8%, 17.0%, and

Table 1. Baseline Characteristics of ischemic stroke patients according to the carotid plaque instability and stenosis degree

	Carotid plaque instability			Carotid stenosis		
	Stable	Unstable	*P* value	None or mild	moderate-severe or occlusion	*P* value
No	38	135		145	28	
Age	67.4 ± 13.7	68.8 ± 10.9	0.49	68.4 ± 11.9	69 ± 9.6	0.81
Men, number (%)	23 (60.5)	91 (67.4)	0.43	92 (63.5)	22 (78.6)	0.12
Smoking, number (%)	14 (36.8)	48 (35.6)	0.88	52 (35.9)	10 (35.7)	0.99
Drinking, number (%)	13 (34.2)	49 (36.3)	0.81	50 (34.5)	12 (42.9)	0.40
Systolic blood pressure (mmHg)	155.7 ± 25.2	152 ± 22.6	0.39	152.6 ± 23.6	154.1 ± 20.7	0.76
Diastolic blood pressure (mmHg)	85.5 ± 14.6	83.4 ± 12.4	0.37	84.6 ± 13.1	80.0 ± 11.4	0.09
Blood glucose (mmol/L)	6.0 ± 1.6	7.2 ± 2.6	< 0.01	6.9 ± 2.5	6.7 ± 2.2	0.71
Total cholesterol (mmol/L)	4.7 ± 1.2	4.7 ± 1.1	0.95	4.7 ± 1.1	4.9 ± 1.2	0.24
Triglycerides (mmol/L)	1.4 ± 1.0	1.5 ± 0.8	0.83	1.4 ± 0.8	1.5 ± 0.7	0.67
HDL cholesterol (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	0.29	1.2 ± 0.3	1.3 ± 0.4	0.79
LDL cholesterol (mmol/L)	2.5 ± 0.7	2.6 ± 0.8	0.47	2.5 ± 0.8	2.7 ± 1.0	0.25
Body mass index (kg/m^2)	24.1 ± 3.8	25.0 ± 3.5	0.22	24.8 ± 3.7	24.9 ± 3.1	0.86
Stroke etiology						
Large vessel atherosclerosis, number (%)	19 (50)	81 (60)	0.27	78 (53.8)	22 (78.6)	0.02
Small vessel occlusive, number (%)	3 (7.9)	20 (14.8)	0.27	20 (13.8)	3 (10.7)	0.89
Cardioembolic, number (%)	14 (36.8)	26 (19.3)	0.02	37 (25.5)	3 (10.7)	0.09
Other, number (%)	0 (0)	2 (1.5)	1.00	2 (1.4)	0 (0)	1.00
Unknown, number (%)	2 (5.3)	6 (4.4)	1.00	8 (5.5)	0 (0)	0.43
History of hypertension, number (%)	18 (47.4)	94 (69.6)	0.01	93 (64.1)	19 (67.9)	0.71
History of diabetes, number (%)	8 (21.1)	48 (35.6)	0.09	49 (33.8)	7 (25.0)	0.36
History of coronary artery disease, number (%)	11 (29)	13 (9.6)	< 0.01	22 (15.2)	2 (7.1)	0.41
History of atrial fibrillation, number (%)	7 (18.4)	15 (11.1)	0.36	19 (13.1)	3 (10.7)	0.97
History of stroke, number (%)	5 (13.2)	28 (20.7)	0.29	26 (17.9)	7 (25.0)	0.38
Admission NIHSS score*	5 (4-9)	5 (3-8)	0.41	5 (3-8)	6 (3-9)	0.52
Time from onset to admission* (hours)	36 (18-72)	24 (15-72)	0.68	24 (18-72)	36 (7-72)	0.67
Pre-stroke antithrombotics treatment, number (%)	2 (5.3)	9 (6.7)	1.00	10 (6.9)	1 (3.6)	0.81
Pre-stroke statin treatment, number (%)	0 (0)	3 (2.2)	0.82	3 (2.1)	0 (0)	1.00
Pre-stroke antihypertensive treatment, number (%)	16 (42.1)	84 (62.2)	0.03	84 (57.9)	16 (57.1)	0.94

*was expressed by median (interquartile range); other continuous variables were expressed by mean ± standard deviation. HDL cholesterol: High density lipoprotein cholesterol; LDL cholesterol: Low density lipoprotein cholesterol; NIHSS: National Institutes of Health Stroke Scale

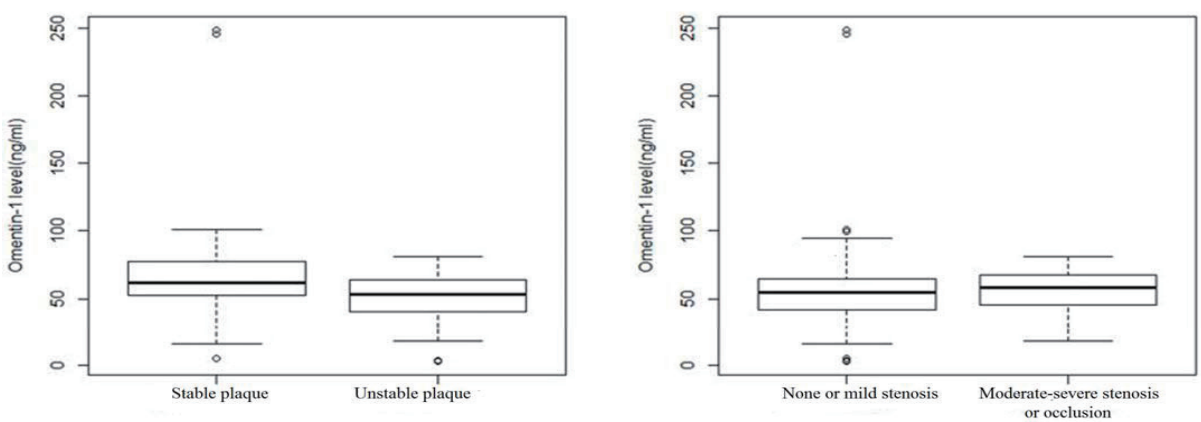

Fig. 1.

A: Boxplots of omentin-1 levels for ischemic stroke patients with stable and unstable carotid plaque; B: Boxplots of omentin-1 levels for ischemic stroke patients with none or mild stenosis and moderate–severe stenosis or occlusion.

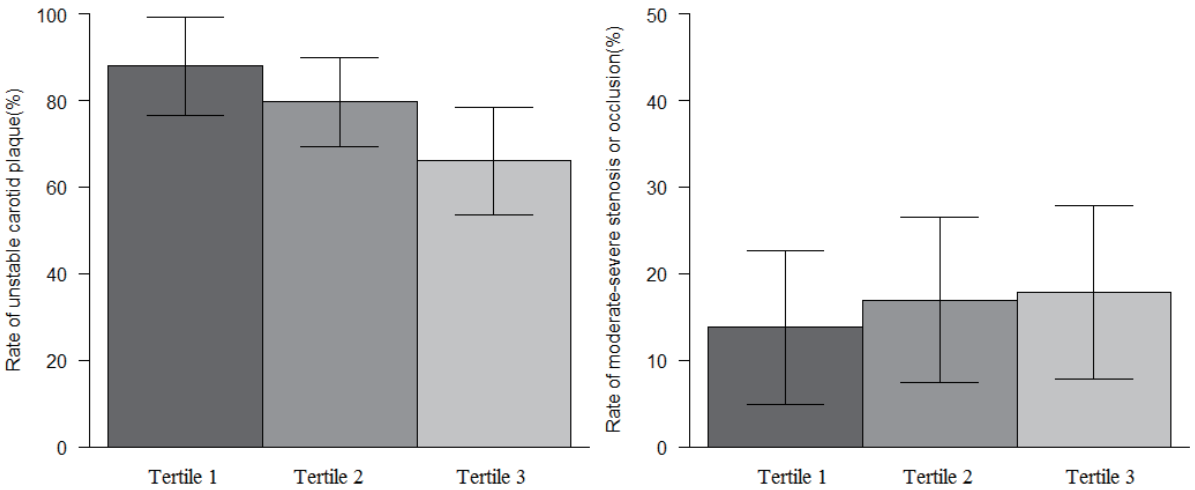

Fig. 2.

A: The rate of unstable carotid plaque for each omentin-1 tertile; B: The rate of moderate–severe stenosis or occlusion for each omentin-1 tertile.

Table 2. Odds ratio and 95% confidence interval for the presence of unstable carotid plaque and moderate-severe stenosis or occlusion according to omentin-1 levels

	The risk of unstable carotid plaque		The risk of moderate-severe stenosis or occlusion	
	Age- and sex- adjusted	Multivariable adjusted*	Age- and sex- adjusted	Multivariable adjusted**
Omentin-1(ng/ml)				
Per log-unit	0.22 (0.07-0.66)	0.25 (0.08-0.79)	1.19 (0.52-2.73)	0.99 (0.39-2.54)
<47.0	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
47.0-61.6	0.53 (0.19-1.48)	0.57 (0.19-1.70)	1.29 (0.47-3.60)	1.30 (0.46-3.68)
≥ 61.6	0.26 (0.10-0.70)	0.31 (0.11-0.91)	1.38 (0.48-3.94)	1.37 (0.48-3.95)
P value for trend	<0.01	0.03	0.55	0.56

*Adjusted for history of hypertension, history of diabetes, history of coronary heart disease, blood glucose level, ischemic stroke subtype and pre-stroke antihypertensive treatment **Adjusted for diastolic blood pressure and ischemic stroke subtype

17.9%, respectively ($P=0.82$).

As shown in **Table 2**, there was a significant association between per-unit increase of log-transformed omentin-1 and risk of unstable carotid plaque. Patients in the highest serum omentin-1 tertile had a significantly decreased risk of unstable carotid plaque compared with the reference group in the age- and sex-adjusted model (OR: 0.26; 95% CI: 0.10–0.70; *P* for trend <0.01). After adjustment for history of hypertension, history of diabetes, history of coronary heart disease, blood glucose level, ischemic stroke subtype and pre-stroke antihypertensive treatment, patients in the highest category of serum omentin-1 had a 0.31-fold risk of unstable carotid plaque compared with the reference group ($P<0.05$) and its trend test was significant (*P* for trend =0.03). However, no significant association between omentin-1 levels and the risk of moderate–severe stenosis or occlusion was observed.

Adding omentin-1 to a logistic regression model consisting of conventional risk factors significantly improved the accuracy of risk prediction for unstable carotid plaque. The IDI (95% CI) was 5.2% (1.2%–9.1%) ($P=0.01$). No significant prediction effect of omentin-1 on moderate–severe stenosis or occlusion was detected as the IDI (95% CI) was 0% (–0.01%–0.02%) ($P=0.69$)

Discussion

This is the first study to investigate the association of serum omentin-1 levels with carotid plaque instability and stenosis degree among acute ischemic stroke patients. Our findings indicate that those with higher omentin-1 levels tend to have a lower risk of unstable plaques. Thus, omentin-1 may be a bio-

marker for predicting carotid plaque instability among acute ischemic stroke patients.

Omentin-1 was previously identified as a novel fat depot-specific secretory protein in a human omental fat cDNA library[2]. Recent studies have reported that omentin-1 may regulate insulin resistance by enhancing insulin-stimulated glucose uptake[2] and suppress vascular inflammation by modulating vascular function and attenuating cyclooxygenase-2 expression[14]. Previous studies have detected a positive association between carotid atherosclerosis and insulin resistance as well as vascular inflammation[15, 16]. Correspondingly, Liu *et al.*[4] reported that omentin-1 levels were significantly decreased in metabolic syndrome subjects with carotid atherosclerosis (10.66 ng/ml) than those metabolic syndrome ones without carotid atherosclerosis (23.48 ng/ml). Another study[5] also demonstrated that the fully adjusted OR (95% CI) for carotid plaque was 0.621 (0.420–0.919) according to the increased level of serum omentin-1 in the multivariable model among type 2 diabetes patients.

Recently, more attention is paid not only to the presence or absence of plaques but also to the plaque instability. Unstable plaques are considered to be high-risk and prone to thrombotic complication Unstable plaques cause ischemic events due to cerebral emboli[17]. Low-level or heterogeneous plaques containing more soft tissue (lipid and/or hemorrhagic core) are thought to be an independent risk factor for ischemic events[18-20]. Unstable plaques share some distinctive features such as a thinner fibrous cap overlying a large necrotic core or a strong intraplaque inflammatory reaction[21, 22]. Novel pro-inflammatory and anti-inflammatory derivatives from adipose tissue, known as adipokines, were found to be associated with carotid plaque instability[23]. For example, Auguet *et al.*[23] reported that visfatin levels were significantly increased in unstable carotid atherosclerotic plaque secretome than in non-atherosclerotic mammary artery secretome. In addition, Gasbarrino *et al.*[24] showed that chemerin was significantly associated with plaque instability. The fully adjusted model, accounting for age, sex, body mass index, high-sensitivity C-reactive protein, type 2 diabetes mellitus, circulating adiponectin, leptin, and resistin, yielded an OR of 0.991 (95% CI: 0.985–0.998) for plaque instability per unit increase in chemerin. These studies were consistent with our findings.

To date, no study has evaluated the association between omentin-1 levels with carotid plaque instability and stenosis degree among acute ischemic stroke patients. In our study, strict quality-control measures were conducted, especially during baseline data collection and carotid atherosclerosis assessment. However, certain limitations of the present study must be mentioned. First, this study was based on a single-center data from a tertiary hospital, and the sample size was relatively small. These characteristics limit the external validity of the findings. Second, omentin-1 levels in our study were determined with a single measurement. Therefore, some exposure misclassification risk is inevitable but is probably low, as previous work demonstrated that serum omentin-1 levels are stable over time[25]. Third, the data about intracranial major artery stenosis from contrast-enhanced magnetic resonance angiography or computer tomographic angiography were not collected in this study. We will analyze the association between omentin-1 levels and intracranial major artery stenosis degree in the future. Furthermore, other adipokines such as vaspin, apelin, visfatin, and ghrelin were not assayed in this study. Hence, the possibility that these adipokines confounded the true association between omentin-1 and carotid atherosclerosis cannot be completely eliminated.

Conclusion

Among ischemic stroke patients, higher omentin-1 levels were inversely associated with carotid plaque instability, but not associated with carotid stenosis degree. Omentin-1 may represent a biomarker for predicting carotid plaque instability of acute ischemic stroke patients.

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Conflict of Interest

None.

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