

Association of serum vaspin, apelin, and visfatin levels and stroke risk in a Chinese case-control study

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Abstract

Adipose tissue acts as an active endocrine organ secreting a number of adipokines and may be involved in biological mechanism of stroke. Vaspin, apelin, and visfatin play important roles in the regulation of vascular disorders.

Our aim was to evaluate whether the concentrations of vaspin, apelin, and visfatin were associated with stroke risk.

A total of 235 patients with stroke (156 patients with ischemic stroke and 79 patients with hemorrhagic stroke) and 235 age- and gender-matched healthy controls were included in this study. A sandwich ELISA was developed to measure the serum vaspin, apelin, and visfatin levels.

There was a statistically significant difference in the median levels of serum vaspin, apelin, and visfatin levels between stroke cases and controls (vaspin: 1.50 vs 1.07 ng/ml; apelin: 1.56 vs 1.32 pg/ml; visfatin: 23.40 vs 19.65 ng/ml; all *P* values <.001). Multiple logistic regression analysis showed that, serum vaspin and visfatin levels were significantly inversely associated with increased risk of stroke, and the odds ratios (ORs) in the highest tertile were 2.25 [95% confidence interval (CI) 1.38–3.67; *P* for trend <.001] for vaspin and 2.56 (95% CI 1.46–4.47; *P* for trend <.001) for visfatin, respectively, compared with the lowest tertile. Higher apelin levels were marginally associated with lower stroke risk (*P* for trend =.060).

Our study indicated that higher vaspin, apelin, and visfatin levels might be associated with increased stroke risk. Necessary prospective cohort studies should be conducted to confirm this association in the future.

Abbreviations: CI = confidence interval, NIHSS = National Institutes of Health Stroke Scale, ORs = odds ratios.

Keywords: adipokines, apelin, stroke, vaspin, visfatin

1. Introduction

Stroke is the second cause of death worldwide and a leading cause of long-term disability in China^[1,2]; however, its pathogenesis is still unknown until now.^[3] Stroke patients occupy lots of medical resources and bring heavy economic pressure and mental burden on patients and families. Stroke shares many risk factors with cardiovascular diseases, such as age, smoking, hypertension, inactivity, overweight or obesity, and dyslipidemia.^[4]

Adipose tissue is a metabolic and active secretory organ that produces a variety of messenger molecules. Adipocyte-derived hormones contribute to the regulation of many biological processes.^[5] Adipokines, like adiponectin and leptin which are the most well-studied. These traditional adipokines play an important role in the pathogenesis of diabetes, dyslipidemia, inflammation, coronary artery disease, and carotid atherosclerosis.^[6,7] The role of novel adipokines in stroke remains largely unknown.^[8]

Emerging evidence suggests associations between novel adipokines such as vaspin, apelin, visfatin between vascular risk factors and atherosclerotic diseases. Vaspin is an important and a new adipokines which mainly produced by adipocytes, and proposed as a biomarker along with other pro-inflammatory adipokines, in evaluating exposure-disease associations.^[9] Vaspin has regulation characteristics in glucose and lipid mechanism. Recent findings illustrate vaspin improves glucose tolerance and insulin sensitivity.^[10] Other study has showed vaspin expression levels were higher in ischemic stroke.^[3,11] Paradoxically, another research has found that ischemic stroke had lower of vaspin serum concentrations.^[12] Apelin encoded by *APLN* gene, is a novel endogenous ligand of the orphan G-protein-coupled receptor.^[13] Some investigations documented the inverse relationship of serum apelin with atherosclerosis.^[14,15] On the contrary, apelin serum levels have been suggested to be increased in patients with coronary atherosclerosis.^[16] However, another report did not find any differences in apelin plasma levels between ischemic stroke patients and healthy controls.^[12] Visfatin mainly secreted by visceral adipose tissue, is a novel adipokine with pleiotropic functions.^[17] Increased serum levels of visfatin have been found

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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in diabetes, obesity, coronary artery disease, and carotid atherosclerosis.^[7,18] Upregulated plasma visfatin levels have been found in ischemic stroke.^[19]

Recent studies showed the novel adipokines may have an important role in the stroke. However, the effect of them on stroke is not yet well understood, and related studies are confusing. Meanwhile, there is less research on the relationship between stroke in the Chinese population. Therefore, in this study, we aimed to investigate the association between serum levels of 3 novel adipokines (vaspin, apelin, and visfatin) and stroke risk in a group of Chinese participants.

2. Methods

2.1. Study population

The study was a case-control study conducted from January 2016 to September 2019. 235 patients with a first stroke were consecutively recruited from the neurology department at 2 hospitals: Chengdu Tianfu New District People's Hospital and Sichuan Provincial People's Hospital. There were 156 patients with ischemic stroke and 79 patients with hemorrhagic stroke. According to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria,^[20] ischemic stroke patients were divided into large-artery atherosclerosis (LAA), small-artery occlusion (SAO), cardioembolism (CE), other determined etiology (SOE), and undetermined etiology, and there were 89 LAA cases, 50 SAO cases, 10 CE cases, 3 SOE cases, and 4 undetermined cases included.

The inclusion criteria were as follows:

- (1) age over 18 years;
- (2) stroke diagnosed according to the World Health Organization criteria, confirmed by CT or MRI;
- (3) no medications were taken before the blood test, and
- (4) stayed in the hospitals no more than 7 days.

Exclusion criteria included patients:

- (1) with a history of cerebral hemorrhage, intracranial space occupying lesions, acute cerebral embolism, lacunar cerebral infarction, coronary heart disease, atrial fibrillation, and malignant tumors; and
- (2) taking any lipid-lowering drugs, anticoagulants, steroids, etc.

The controls were healthy check participants from 2 hospitals mentioned above and were age and gender-matched without a history of cardiovascular diseases.

All participants or their legal representatives gave their informed consent, and study protocol was approved by the ethical committee of Sichuan Provincial People's Hospital.

2.2. Clinical data

Demographic and clinic characteristics were obtained including age, body mass index, education, income, smoking status, hypertension and diabetes mellitus. Smoking was defined as having smoked ≥ 1 cigarette per day for ≥ 1 year. Hypertension was defined as a systolic blood pressure of ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg. Diabetes mellitus was defined as a fasting glucose level ≥ 7.0 mmol/L or postprandial blood glucose ≥ 11.1 mmol/L.

2.3. Vaspin, apelin, visfatin level measurements

Blood samples were collected in siliconized tubes after the admission. The specimens were centrifuged at 1500g for 10

minutes and the separated serum stored at -80°C until laboratory examination.

Vaspin, apelin, and visfatin were analyzed by commercial Human Vaspin ELISA Kit (Cat No: E-EL-H1762c, Elabscience, Wuhan, China), Human Apelin ELISA Kit (Cat No: E-EL-H0456c, Elabscience, Wuhan, China), and Human Visfatin ELISA Kit (Cat No: E-EL-H1763c, Elabscience, Wuhan, China) according to manufacturer's instructions. The absorbance value of the samples was read at 450 nm using a Bio-Rad Model 680 ELISA reader. The concentrations were calculated from the calibrated standard curve, which was constructed using the standards provided in the kit. Each sample was assayed in duplicate, and the level was calculated as the average of the 2 measurements. The laboratory technicians who performed the measurements were blinded to the characteristics of the study participants. The lower detection limits, intra- and inter-assay coefficients of variations (CV%) were 0.1 ng/ml, 6.2% and 8.8% for vaspin, 0.10 ng/ml, 7.5% and 9.4% for apelin, and 3 pg/ml, 8.5% and 10.2% for visfatin, respectively.

2.4. Statistical analysis

Data of normally distributed continuous variables were expressed as the mean value \pm SD, student *t* test was used for comparing parametric data between the groups. Categorical variables were expressed as percentages, and Chi-Squared test was used for comparing classified variables between groups. In further analysis, vaspin, apelin, and visfatin levels were divided into 3 groups according to tertiles.

Conditional logistic regression analyses were performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of stroke. Potential confounders were selected into multivariable adjusted models. In model 1, we only adjusted age. In model 2, we further adjusted BMI, education, income, smoking status, and hypertension and diabetes mellitus. Tests for trend were calculated by including the categorical variables as continuous variables.

Spearman correlation analysis was used to assess the correlation between the vaspin, apelin, and visfatin levels and National Institutes of Health Stroke Scale (NIHSS) scores among stroke cases. Correlation coefficient is represented by r_s .

For statistical analysis, the statistics program SPSS18.0 was used. The values $P < .05$ were considered statistically significant.

3. Results

3.1. Baseline characteristics of patients and matched controls

A total of 235 patients with stroke and 235 age and gender-matching controls were included in our study. Comparing the characteristics of the stroke cases with the controls are described in Table 1. There was no statistically significant difference in the age, BMI, education level, and diabetes mellitus between stroke patients and stroke-free controls ($P > .05$). The income level of the stroke patients group was lower than the control group. 106 (45.11%) patients were smokers in stroke group and in control group were 78 (33.19%), which is significantly higher in stroke patients ($P = .008$). There were 172 (73.19%) hypertension in stroke patients group and 138 (58.72%) in the control group, the hypertension of stroke patients group were significantly higher ($P = .023$).

Table 1
Baseline characteristics of patients and matched controls.

Characteristics	Controls (n=235)	Stroke cases (n=235)	t/χ^2	P
Age, years	57.16 ± 13.38	58.43 ± 10.75	1.134	.260
Body mass index, kg/m ²	23.97 ± 3.14	24.25 ± 3.63	0.894	.372
Education, years, n (%)			1.591	.451
< 6	71 (30.21)	82 (34.89)		
6–12	118 (50.21)	115 (48.94)		
> 12	46 (19.57)	38 (16.17)		
Income, yuan/month/person, n (%)			6.476	.039
≤ 3000	40 (17.02)	62 (26.38)		
3001–6000	87 (37.02)	83 (35.32)		
> 6000	108 (45.96)	90 (38.30)		
Smoking status, n (%)			7.002	.008
Yes	78 (33.19)	106 (45.11)		
No	157 (66.81)	129 (54.89)		
Hypertension, n (%)			5.198	.023
Yes	138 (58.72)	172 (73.19)		
No	97 (41.28)	63 (26.81)		
Diabetes mellitus, n (%)			1.308	.253
Yes	82 (34.89)	94 (40.00)		
No	153 (65.11)	141 (60.00)		
NIHSS score	-	5.24 ± 2.48	-	-
Vaspin, ng/ml	1.07 ± 0.55	1.50 ± 0.79	6.85	<.001
Apelin, ng/ml	1.32 ± 0.58	1.56 ± 0.76	3.85	<.001
Visfatin, pg/ml	19.65 ± 8.34	23.40 ± 8.89	4.75	<.001

Continuous variables were described by means ± SD and categorical variables were described by n (%). NIHSS = National Institutes of Health Stroke Scale.

Mean serum vaspin levels were found to be 1.50 ± 0.79 ng/ml in stroke group compared with 1.07 ± 0.55 ng/ml in control group. Mean serum apelin levels were found to be 1.56 ± 0.76 ng/ml in stroke group compared with 1.32 ± 0.58 ng/ml in control group. Mean serum visfatin levels were found to be 23.40 ± 8.89 pg/ml in stroke group compared with 19.65 ± 8.34 pg/ml in control group. The stroke patients had significantly

higher serum vaspin, apelin and visfatin than control (all P values <.001) (Fig. 1).

3.2. Associations between the serum vaspin, apelin, and visfatin levels and stroke risk

As shown in Table 2, the levels of vaspin, apelin, and visfatin were then grouped according to tertiles. Conditional logistic regression analysis revealed that there was a positive association between serum vaspin and stroke (P for trend <.001). Compared with the lowest tertile of serum vaspin levels, the risk of stroke was significantly increased in the higher 2 tertiles (tertile 2: OR = 1.67, 95% CI: 1.02–2.72; tertile 3: OR = 2.25, 95% CI: 1.38–3.67). As serum apelin levels decreased, stroke risk increased, but this difference was marginally significant (tertile 2: OR = 1.553, 95% CI: 0.949–2.539; tertile 3: OR = 1.618, 95% CI: 0.997–2.625; P for trend = .060). There was a significant positive correlation between serum visfatin levels and stroke (P for trend <.001). With the lowest tertile of serum visfatin level distribution, in the higher 2 tertiles, the risk of stroke was significantly increased (tertile 2: OR = 1.978, 95% CI: 1.107–3.533; tertile 3: OR = 2.557, 95% CI: 1.463–4.471).

Spearman correlation analysis indicated that the NIHSS scores for cases were significantly correlated with levels of vaspin (r_s = 0.219, P = .001), apelin (r_s = 0.198, P = .002), and visfatin (r_s = 0.152, P = .021), respectively.

3.3. Serum vaspin, apelin, and visfatin levels between stroke cases and controls by subtype

Among 235 stroke patients, there were 156 ischemic stroke patients and 79 hemorrhagic stroke patients. We further compared the serum vaspin, apelin, and visfatin levels in ischemic stroke and hemorrhagic stroke. Compared to the corresponding control group, regardless of ischemic stroke patients or hemorrhagic stroke patients, the serum levels of vaspin, apelin, and visfatin were all markedly elevated. And the serum levels of

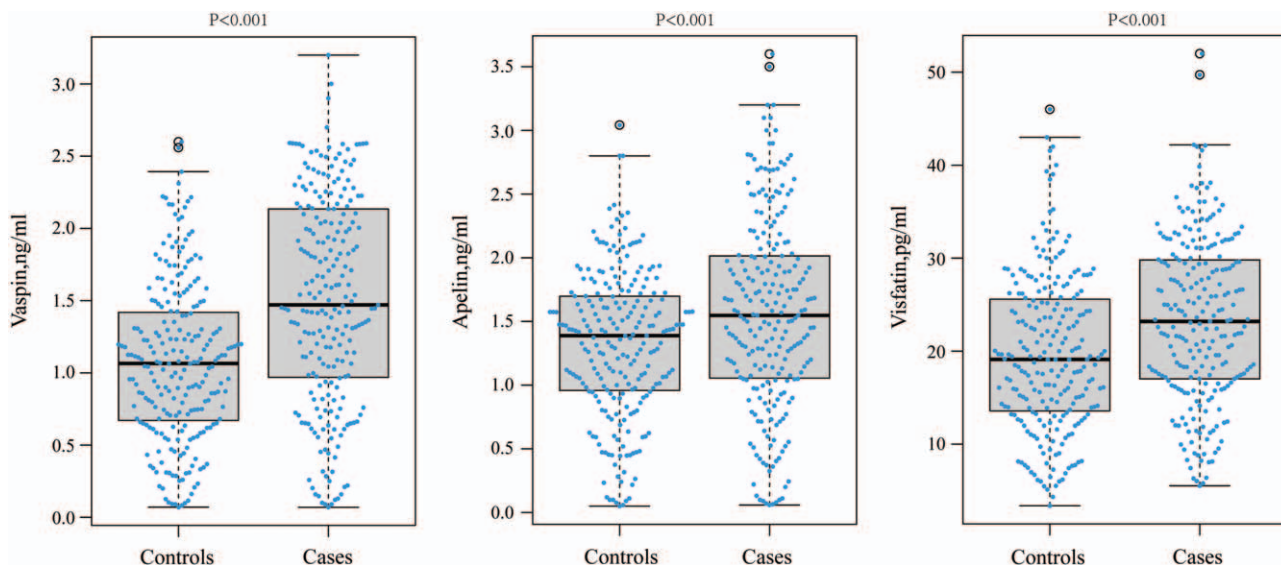


Figure 1. Distribution of serum vaspin, apelin, and visfatin levels among stroke cases and controls.

Table 2
Odds ratio (95% CIs) of stroke risk for tertiles of serum vaspin, apelin, and visfatin.

	Tertiles of serum vaspin, apelin, and visfatin levels		
	T1	T2	T3
Vaspin			
Quartiles, ng/ml	<1.28	1.28–2.01	≥2.01
N (case/control)	42/78	74/79	119/78
OR1 (95% CI) ^a	1.00	1.67 (1.02–2.72)	2.25 (1.38–3.67)
OR2 (95% CI) ^b	1.00	1.62 (1.03–2.54)	2.16 (1.43–3.26)
P		<0.001	
Apelin			
Quartiles, pg/ml	<1.23	1.23–1.97	≥1.97
N (case/control)	55/78	88/79	92/78
OR1 (95% CI) ^a	1.00	1.597 (0.961, 2.653)	1.637 (0.995, 2.693)
OR2 (95% CI) ^b	1.00	1.553 (0.949, 2.539)	1.618 (0.997, 2.625)
P		0.060	
Visfatin			
Quartiles, ng/ml	<15.81	15.81–23.96	≥23.96
N (case/control)	39/78	84/79	112/78
OR1 (95% CI) ^a	1.00	1.978 (1.107, 3.533)	2.557 (1.463, 4.471)
OR2 (95% CI) ^b	1.00	1.835 (1.009, 3.336)	2.469 (1.396, 4.368)
P		<0.001	

BMI = education, income, OR1 = adjusted for age, OR2 = adjusted for age, smoking status, and hypertension and diabetes mellitus.

^a Adjustment for age.

^b Adjustment for age, BMI, education, income, smoking status, hypertension, and diabetes mellitus.

vaspin, apelin, and visfatin in ischemic stroke patients were higher than in hemorrhagic stroke patients (Table 3).

4. Discussion

In this case–control study, vaspin, apelin, and visfatin were significantly higher in the stroke patients compared to control. Higher levels of vaspin, apelin, and visfatin were associated with increased stroke risk. Stratified analysis by stroke subtype shows similar findings.

Stroke has been ranked as the first leading cause of mortality and long-term disability in world and China. As the aging of society and the drastic changes in lifestyle, cerebrovascular disease has become the main disease that endangers the middle-aged and elderly population in China.^[1,2,21] According to epidemiological statistics, about 2 million new strokes occur each year in the country, about 1.5 million people die of cerebrovascular disease each year, and about 6 to 7 million disabled patients, bringing long-term and multifaceted aspects burden to patients, families, and society.^[21,22] At present, there is no ideal curable treatment for cerebrovascular disease. Therefore, it is of great significance to find its risk factors and actively intervene to reduce the incidence. The present study aimed to

explore the serum level vaspin, apelin, and visfatin as predictive biomarkers of stroke for early detection and prevention.

Vaspin is a novel adipokine that was first found by Japanese scholar.^[23] Vaspin is considered to be a member of serine protease family.^[24] There are studies suggesting that there is a relationship between the serum levels of vaspin and stroke. Aust et al^[25] found that the serum vaspin concentration of patients with ischemic cerebrovascular events was lower than that of the normal control group, and further believed that the occurrence of ischemic events was related to the decrease of vaspin serum concentration; and Kadoglou et al^[12] also found that the serum vaspin level were lower in stroke patients with carotid atherosclerosis than control group. However, there were inconsistent results. Cura et al^[11] found that serum vaspin levels in patients with acute stroke were higher than those in the normal control group. In our study, serum vaspin levels were lower in stroke patients than control group. The reason for this contradiction may be the difference in the selected participants in these studies. In Aust and Kadoglou studies, the serum levels of vaspin were lower in the stroke patients with carotid atherosclerosis. However, in our study, we did not specifically classify the diseases and symptoms associated with stroke.

Apelin is a bioactive peptide that was originally identified as the endogenous ligand of the orphan G-protein-coupled receptor. Apelin is widely expressed in the heart, brain, limbs, kidneys, retina, lungs, skin, and adipose tissue.^[26,27] Apelin participate in many physiological activities, such as the regulation of blood pressure, the regulation of myocardial contractility, immunity, glucose metabolism, water balance, cell proliferation, and angiogenesis.^[26,28,29] Apelin signaling pathway is closely related to stroke, especially to regulate a variety of physiological, and pathological processes of ischemic stroke. It promotes the generation of neonatal collateral vessels after ischemic stroke,^[30] inhibits neurons and nerve cell damage,^[31] increase the stability of atherosclerotic plaques^[32] and regulate post-stroke inflammatory response,^[17] and play a neuroprotective role. In this study, we found the serum apelin levels were higher in stroke patients than control group, but the serum apelin levels did not add any diagnostic value of stroke. Recent studies had shown the relationship of the serum levels of apelin and stroke. Differently from our findings, a recently reported study did not find any differences in apelin plasma levels between stroke patients and health controls,^[12] while the author's another report had found the inverse association of apelin serum levels with recent stroke (within 15 days).^[7] They conducted further analysis and found that apelin levels were lower in the stroke patients with carotid atherosclerosis compared to stroke-patients without carotid atherosclerosis.^[12] The differences in apelin serum levels may come from the adopted study subjects and the period of the occurrence of stroke for measuring serum levels. The study found that as different from the time of the occurrence of ischemic

Table 3
Serum vaspin, apelin and visfatin levels between stroke cases and controls by subtype.

	Ischemic Strokes				Hemorrhagic Strokes			
	Stroke cases (n=156)	Controls (n=156)	t	P	Stroke cases (n=79)	Controls (n=79)	t	P
Vaspin, ng/ml	1.59±0.78	1.06±0.54	8.564	<.001	1.32±0.79	1.09±0.57	3.62	<.001
Apelin, pg/ml	1.61±0.74	1.32±0.51	4.947	<.001	1.45±0.79	1.31±0.69	2.046	.042
Visfatin, ng/ml	24.03±8.69	19.62±8.15	5.674	<.001	22.12±9.21	19.72±8.75	2.896	.004

stroke, apelin expression also changed, apelin expression in the ischemic phase of ischemic stroke was increased, while the expression of Apelin during reperfusion is decreased.^[33]

Visfatin is a recently described adipokine highly produced in and secreted by adipose tissue and also produced in animal and human brain,^[34] is also known as nicotinamide phosphoribosyltransferase. Visfatin is expressed in multiple organs, tissues, and cells of the human, such as bone marrow, liver, skeletal muscle cells, kidneys, heart, lungs and immune-active lymphocytes, monocytes, neutrophils.^[35] Visfatin is involved in vital cellular functions such as transcription, translation, cell signaling, and fundamental energy metabolism.^[35,36] Role of visfatin in stroke has been studied and reported by several researches. The increased plasma visfatin levels in acute ischemic stroke had been proved.^[12,37] Visfatin may be an independent risk factor for ischemic stroke.^[19] In our study, we found the similar results that the serum visfatin levels were higher in stroke patients compared to control group. And the increased visfatin levels were especially higher in ischemic group than in the hemorrhagic group. This observation is consistent with a recently report.^[38]

There are some limitations in our research. First, selection bias is difficult to rule out in hospital-based case-control studies. In this study, selection bias was minimized by recruitment of both cases and control groups from a similar target population. Second, the study was a 2-center Cohort and the sample size was relatively small. These characteristics limit the external validity of the findings. Third, serum samples were collected after the cases were diagnosed. The low concentrations may have been a consequence of the stroke. Forth, though we have tried our best to adjust a wide range of potential confounders in our analysis, some residual confounding factors may still remain. For example, factors such as physical activity, parity, family history of obesity were suggested to be associated with obesity,^[39] which may also affect serum adipokine levels, but these factors were not adjusted in our analysis. Finally, the assessment of serum adipokines was based on a single measurement, without taking into account the reliability of measures, which may have caused some misclassification. In addition, we did not have serum levels of adipokines tracking and detection, it is unclear the vaspin, apelin and visfatin persistently changed in response to the stroke.

In conclusion, our data suggested that vaspin, apelin, and visfatin levels might be associated with increased stroke risk. However, the use of serum vaspin, apelin, and visfatin as indicators for stroke needs to be confirmed by further large-scale prospective studies.

Author contributions

Data curation: Dalin Yu.

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Methodology: Dalin Yu, Bin Wu.

Project administration: Bin Huang.

Software: Dalin Yu.

Validation: Bin Wu.

Writing – original draft: Dalin Yu.

Writing – review & editing: Dalin Yu, Bin Huang, Jun Xiao.

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