Co-Effect of Serum Galectin-3 and High-Density Lipoprotein Cholesterol on the Prognosis of Acute Ischemic Stroke

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Goal: The association of combined galectin-3 and high-density lipoprotein cholesterol (HDL-C) with prognosis of acute ischemic stroke remains unknown. This study aimed to evaluate the coeffect of galectin-3 and HDL-C on death and vascular events within 1 year after ischemic stroke. *Materials and Methods:* Based on China Antihypertensive Trial in Acute Ischemic Stroke, a prospective study was conducted among 2970 patients with acute ischemic stroke. The primary outcome was a combination of death and vascular events within 1 year after ischemic stroke. The secondary outcomes were separately those of recurrent stroke, vascular events, and death. *Findings:* The multivariate adjusted hazard ratios (95% confidence intervals) of primary outcome, recurrent stroke, and vascular events were 1.54 (1.07-2.20), 1.78 (1.08-2.95), and 1.92 (1.26-2.94), respectively, in patients with both high galectin-3 and low HDL-C compared to those with both low galectin-3 and high HDL-C. The addition of galectin-3 and HDL-C to conventional factors significantly improved predictive value. Net reclassification index was 15.7% for primary outcome, 18.3% for recurrent stroke, and 20.5% for vascular events. *Conclusion:* Combination of high galectin-3 and low HDL-C was associated with primary outcome, recurrent stroke, and vascular events within 1 year after ischemic stroke, suggesting that the combination of galectin-3 and HDL-C may be used to identify the individuals at risk of poor prognosis after ischemic stroke.

Key Words: Galectin-3—high-density lipoprotein cholesterol—prognosis—ischemic stroke

Introduction

Stroke is the second leading cause of death worldwide and the absolute number of prevalent stroke continues to increase.[1] Thus, efforts are required to identify more effective biomarker, which may help predict and improve the prognosis of patients with stroke.

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Galectin-3, a pleiotropic protein in human body, is an emerging prognostic biomarker for cardiovascular diseases including heart failure[2] and coronary artery disease.[3] In addition, galectin-3 was positively associated with inflammation and oxidative stress,[4] which was major pathological process of ischemic stroke.[5] Previous studies indicated that increased serum galectin-3 was associated with stroke severity and poor functional outcomes,[6] and also with increased risk of 3 months death and major disability after ischemic stroke onset.[7]

High-density lipoprotein cholesterol (HDL-C) is known as an antioxidant that plays a protective role against inflammation and oxidative stress in human body. Several studies showed that HDL-C was inversely associated not only with mortality and vascular events of ischemic stroke,[8-10] but also with galectin-3 level.[11,12] Additionally, a low HDL-C level was associated with poor outcome of heart failure,[13] myocardial infarction,[14] and peripheral arterial disease.[15] However, no studies have specifically investigated the coeffect of galectin-3 and HDL-C on the prognosis of ischemic stroke. This study aimed to evaluate the coeffect of galectin-3 and HDL-C on death, recurrent stroke, and vascular events within 1 year after ischemic stroke onset.

Methods

Study Participants

The study was conducted on the basis of China Antihypertensive Trial in Acute Ischemic Stroke, a multicenter, single-blind, blinded end-points, randomized clinical trial in 26 hospitals in China. The detailed description of the trail design and methods have been published in previous study.[16] Briefly, we recruited 4071 patients aged 22 years or older who had first-ever ischemic stroke confirmed by computed tomography scan or magnetic resonance imaging at hospital admission within 48 hours from onset, and also with an elevated systolic blood pressure (BP) between 140 mm Hg and less than 220 mm Hg from August 2009 to May 2013. Patients were excluded if they (1) had systolic BP greater than or equal to 220 mm Hg or diastolic BP greater than or equal to120 mm Hg; (2) with severe heart failure, acute myocardial infarction, unstable angina, aortic dissection, atrial fibrillation, cerebrovascular stenosis, and resistant hypertension; (3) in deep coma; and (4) treated with intravenous thrombolytic therapy. Those who did not offer blood sample or did not test galectin-3 concentrations were further excluded. Finally, a total of 3082 participants were included in this analysis. This study was approved by the institutional review boards at Soochow University in China and Tulane University in the United States, as well as the ethical committees at the 26 hospitals. Written informed consent was obtained from all study participants or their immediate family members.

Data Collection

Demographic characteristics, lifestyle risk factors, personal history of diseases, and medications were obtained using standard questionnaire by trained staff at the time of enrollment. Stroke severity at baseline was evaluated using National Institutes of Health Stroke Scale (NIHSS) by trained neurologists. Ischemic stroke subtypes were classified as large artery atherosclerosis (thrombosis), cardiac embolism (embolic), and small artery occlusion lacunae (lacunar) in terms of the symptoms and imaging data of the patients.[17]

BP was measured 3 times according to a common protocol adapted from procedures recommended by the American Heart Association.[18] The mean of the 3 measurements was used in analyses. Body weight and height were measured by standard methods and the body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

Fast plasma glucose (FPG) levels were tested using modified hexokinase enzymatic method. Triglyceride (TG), total cholesterol (TC), and HDL-C were analyzed enzymatically using commercial reagents. Low-density lipoprotein cholesterol (LDL-C) levels were assessed using the Friedewald equation. In this study, low and high HDL-C levels were cut off by 1.04 mmol/L according to Chinese guidelines on prevention and treatment of dyslipidemia.[19]

Serum Galectin-3 Concentrations Assessment

Fasting blood samples were collected after at least 8 hours within 24 hours of hospital admission. All plasma and serum samples were separated and frozen at −80°C until laboratory testing. Serum galectin-3 concentrations were tested by laboratory technicians who blinded to the patients' clinical characteristics and outcomes, using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN). The Intra- and interassay coefficients of variation were less than or equal to 3.6% and less than or equal to 6.1%, respectively.

Outcome Assessment

Patients were followed up at 3 months and 1 year after stroke, respectively. The primary outcome was a composite outcome of death and vascular events. The secondary outcomes were separately those of recurrent stroke, vascular events, and death. Deaths from all causes were confirmed by death certificates. Vascular events (ie, vascular deaths, nonfatal stroke, nonfatal myocardial infarction, hospitalized and treated angina, hospitalized and treated congestive heart failure, and hospitalized and treated peripheral arterial disease) and recurrent stroke were abstracted from hospital data.

Statistical Analysis

In this study, galectin-3 was divided into 2 levels based on the median of galectin-3 concentrations: less than 8.65 ng/mL (low galectin-3) and greater than or equal to 8.65 ng/mL (high galectin-3). Then, participants were categorized into 4 groups according to the galectin-3 and HDL-C levels: (1) low galectin-3 and high HDL-C; (2) low galectin-3 and low HDL-C; (3) high galctin-3 and high HDL-C; and (4) high galectin-3 and low HDL-C.

The baseline characteristics were compared across the 4 groups using analysis of variance for continuous variables and chi-square tests for categorical variables. The cumulative risk of primary outcome among 4 subgroups were estimated using Kaplan-Meier curves and compared by log-rank test, respectively. We used 2 multivariate Cox proportional hazards models to compute hazard ratios (HRs) and 95% confidence intervals (95% CIs) of both primary and secondary outcomes across the 4 subgroups. Model 1 adjusted for age, sex, time from onset to hospitalization, FPG, BP, baseline NIHSS scores, current smoking, alcohol drinking, BMI, history of medications (antihypertensive, lipid-lowing, anticoagulant, and antiplatelet drugs), history of diseases (hypertension, chronic heart disease, and diabetes), family history of stroke, ischemic stroke subtype, antihypertensive intervention; model 2 further adjusted for TC, TG, and LDL-C based on model 1. The Spearman's correlation coefficient was used to assess the relationship between galectin-3 and HDL-C. In addition, we calculated the net reclassification index and integrated discrimination improvement to assess the predictive value of combined galectin-3 and HDL-C by comparing a model including galectin-3 and HDL-C and other conventional risk factors with a model including only conventional risk factors.

All P values were 2-tailed, and a significance level of .05 was used. Statistical analyses were conducted using SAS statistical software (version 9.4) and R statistical software (version 3.4.0).

Results

Within 1 year after stroke onset, 112 participants (3.63%) were lost to follow-up. Baseline characteristics of 2970 participants (1896 men, 1074 women, mean age: 62.24 ± 10.82 years) were shown in Table 1. Patients with high galectin-3 level were more likely to be older, nonsmoker, and nondrinker; and had higher level of FPG as well as baseline NIHSS scores. Patients with low HDL-C level tended to be female; had higher rate of hypertension, diabetes as well as BMI and TG level; and they also had lower level of TC and LDL-C.

A total of 263 patients experienced the primary outcome (composite outcome of death and vascular events) and cumulative incidence was 8.86%. There were 131 patients with recurrent stroke (4.41%), 173 patients with vascular events (5.82%), and 169 deaths (5.69%). Patients with coexistence of high galectin-3 and low HDL-C had significantly highest cumulative incidence of primary outcome among 4 groups (log-rank $P < .001$; Fig 1).

As shown in Table 2, coexistence of high galectin-3 and low HDL-C was significantly associated with increased risks of primary outcome, recurrent stroke, and vascular events compared to coexistence of low galectin-3 and high HDL-C, even after adjusting for multiple factors. The hazard ratios (95% CIs) were 1.54 (1.07-2.20) for primary outcome, 1.78 (1.08-2.95) for recurrent stroke, and 1.92 (1.26-2.94) for vascular events. In Figure 2, there was no significant correlation between galectin-3 and HDL-C ($r = -.005$, $P = .776$). Furthermore, add galectin-3 and HDL-C to a model containing conventional risk factors significantly improved predictive value. Net reclassification index was 15.7% for primary outcome ($P = .006$), 18.3% for recurrent stroke ($P = .022$), and 20.5% for vascular events ($P = .004$; Table 3).

Discussion

In this study, we found that high galectin-3 and low HDL-C had a significant coeffect on increased risk of composite outcome of death and vascular events, recurrent stroke, and vascular events within 1 year after ischemic stroke compared with both low galectin-3 and high HDL-C simultaneously, even after adjustment for various potential-confounding factors. Furthermore, addition of galectin-3 and HDL-C to conventional factors significantly improved the reclassification for clinical outcomes in ischemic stroke patients.

Some evidences have demonstrated the prognostic value of galectin-3 for acute and chronic heart failure.[20,21] In addition, galectin-3 concentrations were found to increase in patients with carotid atherosclerosis, and independently be associated with increased risk of cardiovascular mortality in patients with peripheral artery disease.[22] Experimental studies showed that increased galectin-3 could serve as an amplifier of vascular inflammation by recruiting monocytes and enhancing their migration to the artery wall, and stimulating macrophages to release a variety of proinflammatory molecules in atherosclerotic lesions, especially in unstable plaque regions.[23,24] A case-control study showed that galectin-3 was significantly higher in ischemic stroke patients with a poor outcome indicated by mRS scores than those with a good outcome, and galectin-3 inhibition decreased proinflammatory cytokine expression.[6] Moreover, our previous study reported that increased galectin-3 was associated with death and major disability at 3 months after ischemic stroke onset, independent of high-sensitivity C-reactive protein and white blood cell.[7]

Decreased HDL-C has been shown as an important risk factor for cardiovascular events.[25] It is suggested that oxidative stress, which occurs when the increased reactive oxygen species (ROS) over the antioxidant defense, also causes further tissue injury after ischemic stroke.[26] An observational study included 1847 ischemic stroke

Table 1. *Baseline characteristics among ischemic stroke patients according to galectin-3/HDL-C subgroups*

	Low galectin-3		High galectin-3		
	High HDL-C	Low HDL-C	High HDL-C	Low HDL-C	*P* value
No of participants (%)	1099	393	1069	409	
Demographic					
Age, year	60.97 ± 10.36	59.68 ± 10.41	64.20 ± 10.89	63.23 ± 10.96	<.0001
Male (%)	685 (65.74)	279 (76.02)	554 (54.15)	278 (71.83)	.0461
Current smoking (%)	431 (41.36)	175 (47.68)	305 (29.81)	143 (36.95)	<.0001
Alcohol drinking (%)	354 (33.97)	136 (37.06)	282 (27.57)	111 (28.68)	.0007
Clinical features					
Body mass index, kg/m^2	24.76 ± 3.11	25.65 ± 3.22	24.81 ± 3.18	25.21 ± 2.95	<.0001
Systolic BP, mm Hg	166.97 ± 16.96	166.10 ± 17.45	166.70 ± 17.19	165.34 ± 15.60	.5019
Diastolic BP, mm Hg	97.30 ± 10.50	96.81 ± 11.53	96.26 ± 11.37	95.83 ± 10.97	.2402
Fasting plasma glucose, mmol/L	6.48 ± 2.57	6.43 ± 2.37	6.73 ± 2.78	7.13 ± 3.03	.0025
Total cholesterol, mmol/L	5.12 ± 1.06	4.64 ± .94	5.30 ± 1.30	4.75 ± 1.20	<.0001
Triglycerides, mmol/L	1.59 ± 1.16	2.05 ± 1.22	1.89 ± 4.53	2.36 ± 1.59	<.0001
LDL-C, mmol/L	2.95 ± .91	2.80 ± .81	3.07 ± 1.05	2.72 ± .95	<.0001
Baseline NIHSS score	5.33 ± 4.46	4.85 ± 3.88	6.22 ± 5.11	6.05 ± 4.67	<.0001
Time from onset to hospitalization, h	14.69 ± 13.11	15.99 ± 13.45	15.81 ± 13.05	14.41 ± 12.54	.1109
History of diseases (%)					
Hyperlipidemia	63 (6.05)	32 (8.72)	67 (6.55)	31 (8.01)	.2585
Diabetes	145 (13.92)	77 (20.98)	187 (18.28)	101 (26.10)	<.0001
Hypertension	790 (75.82)	305 (83.11)	813 (79.47)	313 (80.88)	.0123
Cardiac heart disease	95 (9.12)	39 (10.63)	128 (12.51)	42 (10.85)	.1025
History of medications (%)					
Antihypertensive drugs	449 (43.09)	184 (50.14)	506 (49.46)	210 (54.26)	<.0001
Lipid-lowing drugs	32 (3.07)	14 (3.81)	28 (2.74)	11 (2.84)	.7715
Antiplatelet drugs	1058 (96.44)	386 (98.22)	1046 (98.03)	395 (96.38)	.0654
Anticoagulant drugs	372 (33.94)	123 (31.30)	395 (37.02)	142 (34.72)	.1872
Ischemic stroke subtype (%)					<.0001
Thrombotic	701 (67.27)	273 (74.39)	789 (77.13)	320 (82.69)	
Embolic	36 (3.55)	5 (1.36)	80 (7.82)	18 (4.65)	
Lacunar	304 (29.17)	89 (24.25)	154 (15.05)	49 (12.66)	
Antihypertensive intervention (%)	519 (49.81)	169 (46.05)	515 (50.34)	207 (53.49)	.2370

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

patients treated by intravenous thrombolysis, demonstrated that lower HDL-C was an independent predictor of 3 months mortality.[27] Low HDL-C was also indicated to be associated with increased risk of composite outcome of all-cause mortality, recurrent stroke, or ischemic heart disease in ischemic stroke patients.[8] Some clinical trials showed that baseline HDL-C could predict recurrent cardiovascular events in acute coronary syndrome after 16 weeks,[28] and raising HDL-C levels with gemfibrozil resulted in a 24% reduction in the combined outcome of death from coronary causes, nonfatal myocardial infarction, and stroke in patients with coronary heart disease.[29] However, no studies investigated the combined effect of high galectin-3 and low HDL-C on death and vascular events in ischemic stroke patients.

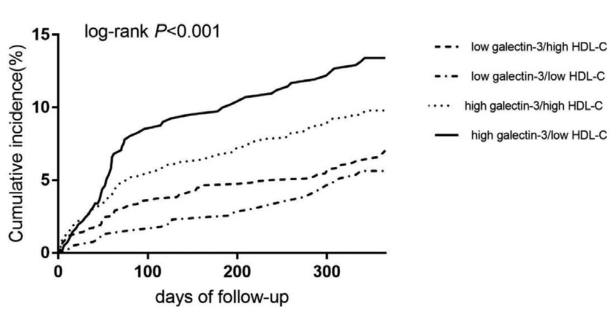

Figure 1. *Cumulative incidence of primary outcome according to galectin-3/HDL-C subgroups.*

Previous studies have showed an inverse relationship between galectin-3 and HDL-C, indicating that galectin-3 may link between dyslipidemia and inflammation.[11,12] Thus, it appears that there is a coeffect of galectin-3 and HDL-C on clinical outcomes of ischemic stroke. Indeed, our study showed that patients with both high galectin-3 and low HDL-C level simultaneously had higher risk of composite outcome of death and vascular events, recurrent stroke, and vascular events within 1 year after ischemic stroke, compared to those with both low galectin-3 and high HDL-C level. The combination of galectin-3 and HDL-C further provided an improved predictive value for prognosis after ischemic stroke. In mechanism, galectin-3 secreted by microglia following brain ischemia

Table 2. *Hazards ratios and 95% confidence interval of 1-year stroke outcome according to galectin-3/HDL-C subgroups*

	Low galectin-3		High galectin-3		
	High HDL-C	Low HDL-C	High HDL-C	Low HDL-C	*P* for trend
Primary outcome					
Composite outcome					
Case (%)	78 (7.12)	22 (5.64)	108 (10.07)	55 (13.35)	
Model 1	1.00 (ref)	.85 (.53-1.38)	1.09 (.80-1.47)	1.57 (1.10-2.23)	.038
Model 2	1.00 (ref)	.86 (.53-1.40)	1.08 (.79-1.46)	1.54 (1.07-2.20)	.032
Secondary outcome					
Recurrent stroke					
Case (%)	43 (3.93)	15 (3.85)	44 (4.10)	29 (7.04)	
Model 1	1.00 (ref)	1.02 (.56-1.86)	.96 (.62-1.49)	1.83 (1.12-2.98)	.042
Model 2	1.00 (ref)	1.00 (.55-1.85)	.97 (.63-1.51)	1.78 (1.08-2.95)	.040
Vascular events					
Case (%)	53 (4.84)	15 (3.85)	62 (5.78)	43 (10.44)	
Model 1	1.00 (ref)	.83 (.46-1.48)	1.03 (.70-1.50)	1.96 (1.29-2.97)	.018
Model 2	1.00 (ref)	.82 (.46-1.47)	1.02 (.70-1.50)	1.92 (1.26-2.94)	.012
Death					
Case (%)	47 (4.29)	13 (3.33)	78 (7.27)	31 (7.52)	
Model 1	1.00 (ref)	.90 (.48-1.68)	1.13 (.78-1.68)	1.34 (.86-2.16)	.216
Model 2	1.00 (ref)	.95 (.50-1.79)	1.12 (.77-1.63)	1.39 (.87-2.23)	.166

Model 1: adjusted for age, sex, time from onset to hospitalization, FPG, baseline NIHSS scores, blood pressure, current smoking, alcohol drinking, BMI, history of medications (antihypertensive, lipid-lowing, anticoagulant, and antiplatelet drugs), history of diseases (hypertension, chronic heart disease, and diabetes), family history of stroke, ischemic stroke subtype, and antihypertensive intervention.

Model 2: further adjusted for total cholesterol, triglyceride, and LDL-C.

contributes to sustained microglia activation through toll-like receptor 4, and prolongs inflammatory response in the brain.[30] Moreover, galectin-3 can act as a scavenger receptor to enhance the phagocytosis of macrophages in taking up oxidized LDL-C, exacerbates atherosclerosis and plaque rupture[31]; in turn, modified lipid-proteins in lipid-rich macrophages also induce galectin-3 overexpression.[32] While HDL-C can block lipids modification in oxidized LDL-C in artery wall cells,[33] and also inhibit oxidized LDL-C-induced monocytes transmigration by 91% and reduce inflammatory situations.[34] Therefore, increased galectin-3 along with low HDL-C level may exacerbate the inflammation and oxidative stress state

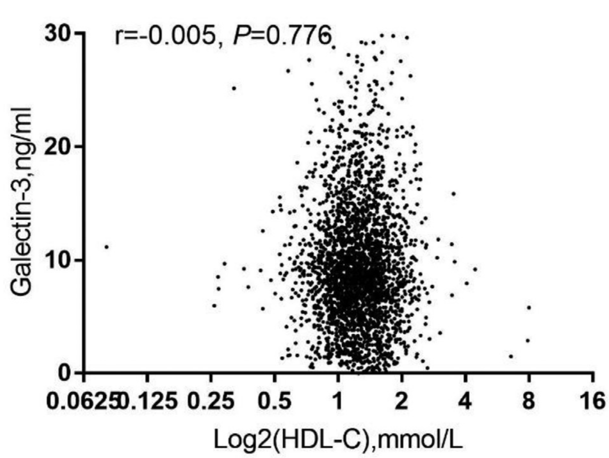

Figure 2. *Spearman's correlation between galectin-3 and HDL-C.*

after ischemic stroke. These findings suggested that galectin-3 should be detected in the acute stage after stroke onset, for the patients with increased galectin-3 and decreased HDL-C simultaneously; reducing galectin-3 and raising HDL-C levels may be beneficial to improve clinical outcomes.

Our study was a prospective cohort study with a large sample size of 2970 acute ischemic stroke patients. Standardized protocols and rigid quality control procedures were used for baseline data collection and outcome assessment during follow-up. Several limitations should be mentioned in our study. First, this study excluded the patients with BP greater than or equal to 220/120 mm Hg and those with intravenous thrombolytic therapy at recruitment. Therefore, the results may not be generalizable to all ischemic stroke patients. However, the proportion of patients with BP greater than or equal to 220/120 mm Hg or treated with intravenous thrombolytic therapy is low in China, and the baseline characteristics of patients included in this study are similar to those from the China National Stroke Registry.[35,36] Second, the number of patients with low HDL-C level was relatively low, which might limited our power to detect significant association of the combined effect of galectin and HDL-C with study outcomes. Third, we did not investigate usage of anticoagulant and antiplatelet drugs in detail that might confound the results during the 1-year follow-up period. However, we believe that this bias is minimal because it is unlikely that participants choose not to take medications because of their galectin-3 and HDL-C levels. Finally, we

Table 3. *Reclassification and discrimination statistics among ischemic stroke patients according to galectin-3/HDL-C subgroups*

	NRI (continuous),%		IDI, %	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Composite outcome				
Model	Reference		Reference	
Model + galectin-3/HDL-C	15.7 (4.5-27.0)	.006	.2(−.1 to .5)	.265
Recurrent stroke				
Model	Reference		Reference	
Model + galectin-3/HDL-C	18.3 (2.6-34.1)	.022	.3 (−.1 to .7)	.061
Vascular events				
Model	Reference		Reference	
Model + galectin-3/HDL-C	20.5 (6.5-34.5)	.004	.6 (−.2 to 1.0)	.008
Death				
Model	Reference		Reference	
Model + galectin-3/HDL-C	8.9 (−4.4 to 22.3)	.189	.02 (−.1 to .2)	.805

Abbreviations: IDI, integrated discrimination index; NRI, net reclassification index.
Model: adjusted for the same variables as model 2 in Table 2.

did not conduct serial measurements of serum galectin-3 and HDL-C concentrations; thus the association between galectin-3 and HDL-C changes and clinical outcomes in acute ischemic stroke patients could not be examined.

In summary, both high galectin-3 and low HDL-C were associated with risk of composite outcome of death and vascular events, recurrent stroke, and vascular events within 1 year after ischemic stroke, suggesting that the combination of galectin-3 and HDL-C should be used to identify the individuals at risk of poor prognosis after ischemic stroke.

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Conflicts of Interest

The authors declare that they have no competing interests.

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