Original Article

Dyslipidemia and Outcome in Patients with Acute Ischemic Stroke*

XU Tian[1], ZHANG Jin Tao[2], YANG Mei[3], ZHANG Huan[1], LIU Wen Qing[2], KONG Yan[2], XU Tan[1], and ZHANG Yong Hong[1,#]

1. Department of Epidemiology, School of Public Health, Medical College of Soochow University, Suzhou 215123, Jiangsu, China; 2. Department of Neurology, Chinese PLA 88 Hospital, Tai'an 271000, Shandong, China; 3. Department of Ophthalmology, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu, China

Abstract

Objective To study the relationship between dyslipidemia and outcome in patients with acute ischemic stroke.

Methods Data about 1 568 patients with acute ischemic stroke were collected from 4 hospitals in Shandong Province from January 2006 to December 2008. National Institute of Health Stroke Scale (NIHSS) >10 at discharge or death was defined as the outcome. Effect of dyslipidemia on outcome in patients with acute ischemic stroke was analyzed by multivariate logistic regression analysis and propensity score-adjusted analysis, respectively.

Results The serum levels of TC, LDL-C, and HDL-C were significantly associated with the outcome in patients with acute ischemic stroke. Multivariate logistic regression analysis and propensity score-adjusted analysis showed that the ORs and 95% CIs were 3.013 (1.259, 7.214)/2.655 (1.298, 5.43), 3.157 (1.306, 7.631)/3.405 (1.621, 7.154), and 0.482 (0.245, 0.946)/0.51 (0.282, 0.921), respectively, for patients with acute ischemic stroke. Hosmer-Lemeshow goodness-of-fit test showed no significant difference in observed and predicted risk in patients with acute ischemic stroke (chi-square=8.235, *P*=0.411).

Conclusion Serum levels of TC, LDL-C, and HDL-C are positively related with the outcome in patients with acute ischemic stroke.

Key words: Dyslipidemia; Acute ischemic stroke; Outcome; Multivariate logistic regression analysis; Propensity score-adjusted analysis

Biomed Environ Sci, 2014; 27(2): 106-110 *doi: 10.3967/bes2014.023* *ISSN: 0895-3988*

www.besjournal.com (full text) *CN: 11-2816/Q*

INTRODUCTION

Stroke is a leading cause of long-term worldwide[1] and the second most common cause of death in China, accounting for nearly 20% of all deaths in both rural and urban settings[2]. Dyslipidemia is a major risk factor for cardiovascular diseases[3-4]. Most studies have focused on the relationship between serum level of lipid and incidence of ischemic stroke,

*This study was supported by the National Natural Science Foundation of China (Grant No. 81172761) and a Project of the Priority Academic Program Development of Jiangsu Higher Education Institutions.

#Correspondence should be addressed to: ZHANG Yong Hong, Professor, MD, PhD, Tel: 86-512-65880078, E-mail: yhzhang@suda.edu.cn

Biographical note of the first author: XU Tian, male, born in 1984, MD, PhD, majoring in cardiovascular and cerebrovascular diseases epidemiology.

Received: May 7, 2013; Accepted: July 25, 2013

but their findings are inconsistent[5-8]. Few studies are available on the relationship between serum lipid level and outcome in patients with ischemic stroke.

Considering the low outcome incidence rate, excessive number of confounding factors and potential collinearity in this study, multivariable logistic regression analysis may not be ideal for estimating the exposure effects[9]. Instead, propensity score-adjusted analysis can be used in these situations since propensity score is a conditional probability which is treated as a composite confounding factor in multivariate logistic regression analysis[10-11] .

MATERIALS AND METHODS

Study Participants

This study was conducted from January 1 of 2006 to December 31 of 2008 in acute ischemic stroke patients with their diagnosis established by CT or MRI. The study was approved by Ethics Committee of Soochow University Public Health School.

Data Collection

Baseline data were collected within 24 h after admission by interview with the patients or their family members. Demographic data, life-style risk factors, medical history, clinical laboratory tests, and CT and MRI data were collected using a standard questionnaire. Blood pressure was measured within 30 min after admission, the study participants were placed in the supine position as previously described[12]. The patients with acute ischemic stroke were assessed at admission and discharge according to the NIHSS[13].

Blood samples were taken from the patients within 24 h after admission. Plasma glucose levels were measured as previously described[14]. Serum levels of TC, HDL-C, and TG were measured with the Beckman Synchron CX5 Delta Clinical System (Beckman Coulter, Inc., Fullerton, California, USA)[15] . Serum LDL-C level was measured according to the Friedewald equation[16].

Statistical Analysis

The continuous and categorical variables were calculated for NIHSS≤10 at discharge and NIHSS>10 / death. *P* values were calculated by analysis of variance for the difference in mean of continuous variables, and by χ^2 test or Fisher exact test for the difference in categorical variables.

The cut-points of TC, TG, LDL-C, and HDL-C was ≥6.22 mmol/L, ≥2.26 mmol/L, ≥4.14 mmol/L, and <1.04 mmol/L, respectively, in patients with acute ischemic stroke according to the Chinese guidelines on prevention and treatment of dyslipidemia in adults (2007)[17]. The dichotomous variable was used as the outcome based on NIHSS>10/death or NIHSS≤10 at discharge while the serum levels of TC, TG, HDL-C, and LDL-C were used as the binary exposure variables. The covariates including age, gender, alcohol consumption, cigarette smoking, systolic and diastolic blood pressure, fasting glucose level, admission NIHSS, history of stroke, hypertension, diabetes, coronary and rheumatic heart disease, atrial fibrillation and lipid levels depending on the exposure variables were adjusted in multivariate logistic regression analysis. The effect of dyslipidemia on outcome in patients with ischemic stroke was also analyzed by propensity score-adjusted analysis. The propensity score was calculated based on the covariates and divided into 5 quintiles. Integration of a propensity score by 5 quintiles into the analysis may provide more comparability between covariate distributions[9]. The significant dyslipidemia components and other risk factors including age, gender, blood pressure, fasting glucose level, atrial fibrillation history and admission nihss were analyzed to predict outcome incidence rate. Model calibration was assessed by Hosmer–Lemeshow goodness-of-fit test. *P* values were two-tailed and $P<0.05$ was considered significantly different. All statistical analyses were conducted using SAS statistical software (version 9.2) and R statistical package (version 2.15), respectively.

RESULTS

A total of 1 568 patients with acute ischemic stroke were included in this study. The demographic and clinical data are shown in Table 1. The age, fasting glucose level and incidence of atrial fibrillation history were higher in patients with their NIHSS>10 at discharge or death than in those with their NIHSS<10 at discharge. Marginal significant difference was observed in systolic blood pressure between the two groups. Figure 1 shows the outcome incidence rate in patients with ischemic stroke according to different lipid levels. The outcome

was poorer in patients with abnormal TC and LDL-C than in those with normal TC and LDL-C.

The serum levels of TC, LDL-C, and HDL-C were significantly related with the outcome in patients with acute ischemic stroke (Table 2). Multivariate logistic regression analysis and propensity score-adjusted analysis showed that the ORs and 95%CIs were 3.013 (1.259, 7.214)/2.655 (1.298, 5.43), 3.157 (1.306, 7.631)/3.405 (1.621, 7.154), and 0.482 (0.245, 0.946)/0.51 (0.282, 0.921), respectively, for the patients with acute ischemic stroke. A more precise parameter was achieved by propensity score-adjusted analysis than by multivariate logistic regression analysis[18].

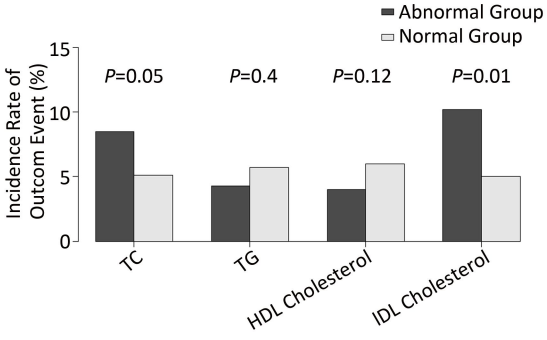

Figure 1. Outcome incidence rate in patients with ischemic stroke according to different lipid levels (*P* values were calculated by χ^2 test).

Table 1. Parameters about 1 568 Patients with Ischemic Stroke According to Their Outcome at Discharge

Items	NIHSS>10 at Discharge or Death	NIHSS≤10 at Discharge	*P* Value
No.	86	1 482	
Age (years)	67.62±11.72	63.81±12	0.004
Men, No. (%)	54 (62.8)	949 (64)	0.815
Cigarette smoking, No. (%)	26 (30.2)	404 (27.3)	0.548
Alcohol consumption, No. (%)	21 (24.4)	359 (24.2)	0.967
Systolic blood pressure (mmHg)	151.56±28.09	145.69±21.69	0.060
Diastolic blood pressure (mmHg)	90.95±15.93	88.46±13.57	0.101
Total cholesterol (mmol/L)	4.92±1.24	4.99±1.11	0.602
Triglycerides (mmol/L)	1.41±1.08	1.56±1.13	0.228
HDL cholesterol (mmol/L)	1.27±0.35	1.26±0.35	0.879
LDL cholesterol (mmol/L)	2.98±1.05	2.99±0.87	0.981
Fasting glucose (mmol/L)	7.51±3.71	6.39±2.69	0.007
Admission NIHSS	12.86±8.27	3.75±4.91	<0.001
History of hypertension, No. (%)	57 (66.3)	941 (63.5)	0.602
History of diabetes, No. (%)	13 (15.1)	237 (16)	0.829
History of coronary heart disease, No. (%)	15 (17.4)	211 (14.2)	0.411
History of atrial fibrillation, No. (%)	10 (11.6)	44 (3.0)	<0.001
History of stroke, No. (%)	31 (36)	521 (35.2)	0.866
History of rheumatic heart disease, No. (%)	1 (1.2)	15 (1.0)	0.596*

Note. *Fisher exact test.

Table 2. ORs and 95% CIs for Outcome in Patients with Acute Ischemic Stroke According to Different Lipid Levels

Analysis	Coefficient Estimations	Standard Errors	OR (95% CI)
TC (≥6.22 mmol/L *vs* < 6.22 mmol/L)			
Multivariate logistic regression analysis	1.1030	0.4454	3.013 (1.259, 7.214)
Propensity score-adjusted analysis	0.9764	0.3651	2.655 (1.298, 5.43)
TG (≥2.26 mmol/L *vs* <2.26 mmol/L)			
Multivariate logistic regression analysis	-0.1248	0.4153	0.883 (0.391, 1.992)
Propensity score-adjusted analysis	0.1094	0.3739	1.116 (0.536, 2.322)
LDL-C (≥4.14 mmol/L *vs* <4.14 mmol/L)			
Multivariate logistic regression analysis	1.1495	0.4504	3.157 (1.306, 7.631)
Propensity score-adjusted analysis	1.2253	0.3787	3.405 (1.621, 7.154)
HDL-C (<1.04 mmol/L *vs* ≥1.04 mmol/L)			
Multivariate logistic regression analysis	-0.7306	0.3445	0.482 (0.245, 0.946)
Propensity score-adjusted analysis	-0.6738	0.3015	0.51 (0.282, 0.921)

A model including serum TC, LDL-C , HDL-C, age, gender, blood pressure, fasting glucose level, atrial fibrillation history and admission NIHSS was established. Model calibration using the Hosmer-Lemeshow goodness-of-fit test yielded a chi-square of 8.235 (P=0.411), indicating no significant difference in observed and predicted risk between the two groups (Figure 2).

DISCUSSION

In this study, the serum levels of TC, LDL-C, and HDL-C were related with the outcome in patients with acute ischemic stroke.

Dyslipidemia is a major risk factor for coronary heart disease (CHD) and its role in the pathogenesis of ischemic stroke is still unclear[19]. It was reported that the serum levels of TC, LDL-C, and HDL-C were related with the risk factors for ischemic stroke[5-8]. In this study, the outcome of patients with ischemic stroke was related with their serum levels of TC and LDL-C , rather than with their serum TG level, which is similar with those in previous studies. The low serum HDL-C level was a protective factor for the outcome in patients with acute ischemic stroke in the present study.

HDL-C, an antioxidant, plays an important role in the pathogenesis of acute ischemic stroke by inhibiting the oxidation of phospholipid and the activity of minimally modified LDL[20-21]. It is well established that augmenting the levels and/or function of HDL and its apolipo-proteins can protect major blood vessels against injury. However, HDL particles can also assume pro-inflammatory and pro-atherogenic characteristics, especially when an acute phase or chronic systemic inflammatory response is present[22]. HDL exerts no effect in patients with atherosclerosis but increases formation of lipid peroxide and oxidation of LDL and phospholipids in patients with a history of CHD[23], which is likely a reasonable explanation for the discrepancy between the findings in this study and other studies.

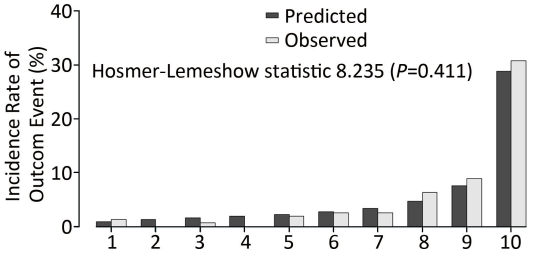

Figure 2. Observed and predicted outcome incidence rate in patients with acute ischemic stroke (P=0.411).

Oxidized cholesterol, particularly LDL cholesterol, initiates inflammation and forms plaques in blood vessel wall, which inhibits blood flow in arteries. LDL cholesterol is a stronger oxidation reaction factor[24] than TC and HDL-C, and controlling the LDL-C level in patients with acute ischemic stroke at admission can improve their prognosis.

In conclusion, the serum levels of TC, LDL-C, and HDL-C are positively related with the outcome in patients with acute ischemic stroke.

There are several important strengths of our study. First, it is the largest study in the Chinese population to show the relationship between dyslipidemia and outcome in patients with acute ischemic stroke with its findings validated by propensity score-adjusted analysis and multivariate logistic regression analysis. Second, the severity of stroke at admission was adjusted as an important covariate, which reflected that the serum levels of TC, LDL-C, and HDL-C were the independent risk factors for the outcome in patients with acute ischemic stroke.

REFERENCES

1. WHO. The top 10 causes of death. Geneva, Switzerland: World Health Organization. 2008.
2. Heeley E, Anderson CS, Huang Y, et al. Role of health insurance in averting economic hardship in families after acute stroke in China. Stroke, 2009; 40, 2149-56.
3. Kostis JB. The importance of managing hypertension and dyslipidemia to decrease cardiovascular disease. Cardiovasc Drugs Ther, 2007; 21, 297-309.
4. Grover SA, Coupal L, Kaouache M, et al. Preventing cardiovascular disease among Canadians: what are the potential benefits of treating hypertension or dyslipidemia? Can J Cardiol, 2007; 23, 467-73.
5. Kurth T, Everett BM, Buring JE, et al. Lipid levels and the risk of ischemic stroke in women. Neurology, 2007; 68, 556-62.
6. Shahar E, Chambless LE, Rosamond WD, et al. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Stroke, 2003; 34, 623-31.
7. Sturgeon JD, Folsom AR, Longstreth WT, et al. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke, 2007; 38, 2718-25.
8. Everett BM, Kurth T, Buring JE, et al. The relative strength of C-reactive protein and lipid levels as determinants of ischemic

stroke compared with coronary heart disease in women. J Am Coll Cardiol, 2006; 48, 2235-42.
9. Little RJ and Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. Annu Rev Public Health, 2000; 21, 121-45.
10. Rosenbaum PR and Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika, 1983; 70, 41-55.
11. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med, 1998; 17, 2265-81.
12. Perloff D, Grim C, Flack J, et al. Human blood pressure determination by sphygmomanometry. Circulation, 1993; 88, 2460-70.
13. Khatri P, Hill MD, Palesch YY, et al. Methodology of the Interventional Management of Stroke III Trial. Int J Stroke, 2008; 3, 130-7.
14. Sitzmann FC and Eschler P. Enzymatic determination of blood glucose with a modified hexokinase method. Med Klin, 1970; 65, 1178-83.
15. Roeschlau P, Bernt E, and Gruber W. Enzymatic determination of total cholesterol in serum. Z Klin Chem Klin Biochem, 1974; 12, 226.
16. Friedewald WT, Levy RI, and Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem, 1972; 18, 499-502.
17. Union Committee Chinese guidelines on prevention and treatment of dyslipidemia in adults. Zhonghua Xin Xue Guan Bing Za Zhi, 2007; 35, 390-419. (In Chinese)
18. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med, 1997; 127, 757-63.
19. Amarenco P and Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet Neurol, 2009; 8, 453-63.
20. Watson AD, Berliner JA, Hama SY, et al. Protective effect of high density lipoprotein associated paraoxonase. Inhibition of the biological activity of minimally oxidized low density lipoprotein. J Clin Invest, 1995; 96, 2882-91.
21. Navab M, Berliner JA, Subbanagounder G, et al. HDL and the inflammatory response induced by LDL-derived oxidized phospholipids. Arterioscler Thromb Vasc Biol, 2001; 21, 481-8.
22. Fogelman AM. When good cholesterol goes bad. Nat Med, 2004; 10, 902-3.
23. Ansell BJ, Navab M, Hama S, et al. Inflammatory/antiinflammatory properties of high-density lipoprotein distinguish patients from control subjects better than high-density lipoprotein cholesterol levels and are favorably affected by simvastatin treatment. Circulation, 2003; 108, 2751-6.
24. Adibhatla RM and Hatcher JF. Lipid oxidation and peroxidation in CNS health and disease: from molecular mechanisms to therapeutic opportunities. Antioxid Redox Signal, 2010; 12, 125-69.