

Received: 2015.01.22
Accepted: 2015.02.25
Published: 2015.06.29

Paradoxical Elevation of High Density Lipoprotein Cholesterol in Association with Lacunar-Type Cerebral Infarction

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AEF **Gui-Lin Meng***
BCD **Yan Tan***
BCD **Min Fang**
BCD **Hong-Yan Yang**
AG **Xue-Yuan Liu**
BCD **Yan-Xin Zhao**

Department of Neurology, Tenth People's Hospital, Tongji University, Shanghai, P.R. China

* Equal contributors

Corresponding Author: Xue-Yuan Liu, e-mail: liu1304@yeah.net and Yan-Xin Zhao, e-mail: zhaoyanxindd@126.com

Source of support: National Natural Science Foundation of China (81171163, 81171023); Shanghai Science and Technology Committee Project (11411950303, 11DZ1920903)

Background: The aim of this study was to evaluate the association between high-density lipoprotein cholesterol (HDLC) levels and the risk of lacunar infarction (LI) in a retrospective cohort study in China.

Material/Methods: We recruited 229 patients with obsolete brain infarctions single side (SOBI), 218 with obsolete brain infarctions bilateral sides (BOBI), 193 with both acute stroke and obsolete lacunar infarctions single side (AI&SOBI), 113 with both acute stroke and obsolete lacunar infarctions bilateral sides (AI&BOBI), and 203 without any infarctions (Control).

Results: 1) The plasma levels of HDLC in group BOBI, AI&SOBI, and AI&BOBI were higher than in the control group, and lower in group SOBI than in the control group ($p < 0.01$). 2) The plasma levels of HDLC in group AI&SOBI were significantly higher than in group SOBI ($p < 0.01$). 3) The plasma levels of HDL were similar between group AI&SOBI and AI&BOBI. 4) There were significant relationships between HDLC and acute lacunar stroke, even after adjusting for these factors such as age, sex, triglyceride, total cholesterol, low-density lipoprotein cholesterol, and history of diabetes ($p = 0.001$). 4) Compared with the controls, the calculation of odds ratios indicated relative risk estimates of higher HDLC for acute lacunar stroke with obsolete lacunar infarction.

Conclusions: Elevated HDLC may be an independent predictor of recurrent stroke with obsolete lacunar infarctions single side in Chinese people, justifying clinical trials for secondary prevention of stroke by generally increasing HDL level. According to the difference between single and bilateral side multiple silent lacunar infarcts, it is inferred that HDLC may increase the risk of atherothrombotic infarction but reduce the risk of cardioembolic infarction in the general Chinese population.

MeSH Keywords: **Cholesterol, HDL • Risk Factors • Stroke, Lacunar**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/893647>



2220



3



—



42



Background

Stroke is a major healthcare problem and a serious economic burden to society [1–4]. In China, stroke is the second leading cause of death. Currently, more than 7 million individuals suffer from stroke. There are 2 million individuals with newly diagnosed stroke each year, moreover, about 1.2–1.5 million die of cerebrovascular disease, with 75% of survivors suffer from long-term disability, and 40% even suffer from severe disability [5,6].

Numerous studies have demonstrated that stroke risk was related to low density lipoprotein cholesterol (LDLC), while less attention has been paid to the effects of high-density lipoprotein cholesterol (HDLC) levels on the risk of stroke. Some epidemiological studies have suggested a protective effect of HDLC on stroke, whereas other studies have found no or a weaker association [7–12]. It is unclear whether this contradiction happens because of coincidence or different roles of HDLC playing according to accurate types of stroke, because researches targeted at accurate stroke types such as lacunar strokes are seldom. From the studies previous, data are confusing and conflicting, so actual local studies are required to clarify this relationship regionally and guide clinical work. As we all know, Asian populations have lower adiposity and insulin resistance than Western populations [13].

Lacunar strokes constitute about 20–25% of ischemic strokes. Although lacunar strokes occasionally result from mechanisms of brain ischemia such as cardiogenic embolism or carotid-artery stenosis, most are attributed to disease of penetrating branches of large cerebral arteries. This underlying disorder is the most frequent cause of covert brain infarcts and vascular cognitive impairment [14–19]. Some patients with lacunar infarction have to face the risk of recurrent infarction, which poses the question how the HDLC functions in the pathophysiology and more importantly, determining prognosis and treatment. The correlation of HDLC and lacunar strokes needs to be confirmed by strict scientific proof. The purpose of this retrospective study was to evaluate the association between HDLC and lacunar infarction.

Material and Methods

Selection of patients

Between August 1, 2013 to August 1, 2014 consecutive patients diagnosed with acute lacunar infarction or patients confirmed to have no signs of stroke visited the Department of Neurology, Shanghai Tenth People's Hospital, were enrolled in our study.

The inclusion criteria met the diagnostic criteria set in the first edition of the Chinese Guidelines for Cerebrovascular Disease

Prevention and were confirmed by magnetic resonance imaging examinations: 1) Patients were eligible for participation in the study if they were 50 years of age or older, had experienced a symptomatic lacunar stroke or no signs of stroke. Symptoms of lacunar stroke consist of one of the recognized lacunar syndromes (pure motor stroke, clumsy hand dysarthria, ataxic hemiparesis, and pure sensory or sensorimotor stroke) in the absence of cortical deficits. 2) They should not have major risk factors for cardioembolic sources of stroke. 3) Besides, participants with a clinical acute lacunar syndrome were required to meet MRI criteria that included a lesion measuring 2.0 cm or less in diameter on diffusion-weighted imaging that corresponded to a positive apparent-diffusion-coefficient image or a lesion with a well-delineated area of focal hyperintensity imaging that corresponded to the clinical syndrome.

The exclusive criteria should be as follows: 1) Patients with metallic implants. 2) Patients diagnosed with other types of stroke but not acute lacunar infarction. 3) Previous intracranial hemorrhage (with the exception of traumatic hemorrhage) or cortical ischemic stroke. 4) Patients with severe cardiovascular disease, renal insufficiency, liver dysfunction, neoplastic or chronic disease.

All participants underwent cranial magnetic resonance imaging scans (MRI) to assess lacunar infarction, other subtypes of stroke, or normal image. The MRI in our hospital were primarily obtained using a 1.5 T scanner (Philips, Eindhoven, Noord-Brabant, Netherlands) and a 3.0 T scanner (Siemens, Erlangen, Bavaria, Germany). The MRI protocol consisted of a T1-weighted image [repetition time/echo time (TR/TE)=101/1.92 for the 1.5 T scanner and 2000/9 for the 3.0 T scanner], fluid attenuated inversion recovery images (FLAIR) (TR/TE=6000/110 for the 1.5 T scanner and 8500/94 for the 3.0 T scanner), DWI (TR/TE = 3393/86 for the 1.5 T scanner and 6000/94 for the 3.0 T scanner) in the axial plane, and a T2-weighted image (TR/TE=1940/120 for the 1.5 T scanner and 4540/96 for the 3.0 T scanner) in the sagittal plane with 16 layers. Besides MRI, the patients underwent blood examinations in a fasting state, including hemoglobin (Hb), C reactive protein (CRP), blood glucose, HDLC, low density lipoprotein cholesterol (LDLC), triglyceride (TG), and total cholesterol (TC). Multivariate logistic regression analyses were performed to examine the relationship between HDLC and infarction.

Ethics statement

The study had the approval of the ethics committee of the Tenth People's Hospital, Shanghai, China.

Assessment of potential covariates at baseline

A record of clinical history was used to obtain information on enrolled subjects, including age, gender, body mass index

Table 1. Baselines characteristics of the different groups.

	SOBI (n=229)	BOBI (n=218)	AI & SOBI (n=193)	AI & BOBI (n=113)	Control (n=203)
Male (%)	121 (52.83%)	126 (57.80%*)	95 (49.22%)	57 (50.44%)	102 (50.24%)
Age (years)	66.60±12.49	72.04*±12.33	59.34±10.78	68.65±10.93	64.88±12.66
Body mass index (kg/m ²)	24.44±3.25	27.36±3.31	23.90±3.03	28.42±2.97	24.50±3.55
Current smoking (%)	81 (35.37%)	73 (33.48%)	72 (37.31%)	42 (37.16%)	60 (29.56%)
Alcohol intake (%)	75 (32.76%)	64 (29.36%)	66 (34.20%)	38 (33.63%)	59 (29.06%)
Hypertension (%)	159 (69.43%)	159 (72.94%)	145 (75.13%*)	87 (76.99%*)	134 (66.00%)
Diabetes (%)	40 (17.47%)	55 (25.23%)	62 (32.12%)	39 (34.51%*)	32 (15.76%)
Hyperhomocysteinemia (%)	35 (15.28%)	43 (19.72%)	85 (44.04%**)	56 (49.56%**)	20 (9.85%)
Total cholesterol (mg/dl)	4.38±1.08	4.81±1.06	4.62±0.98	4.92±0.87	5.23±1.22
Triglycerides (mg/dl)	1.64±1.10	1.94±1.03	0.82±0.52	1.20±0.94	1.22±1.10
LDLC (mg/dl)	2.84±0.45	2.67±0.77	3.17±0.50	2.80±0.67	3.20±0.80

* Means $p < 0.05$; ** means $p < 0.01$ vs. control group; SOBI – obsolete brain infarctions single side; BOBI – obsolete brain infarctions bilateral sides; AI&SOBI – acute stroke and obsolete lacunar infarctions single side; AI&BOBI – acute stroke and obsolete lacunar infarctions bilateral sides.

(BMI), hypertension, diabetes, smoking, and medications prescribed by physicians. Smoking status was classified into “non-smoking” and “smoking” according to self-reported information. Weight and height were measured during the hospital and BMI was calculated as weight (kg)/height (m)². Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice in the seated position using a mercury sphygmomanometer. The average of two readings was used in the analyses. Hypertension was defined based on: personal history of hypertension, a SBP ≥ 140 mmHg, a DBP ≥ 90 mmHg, or currently taking antihypertensive medication prescribed by a physician. The average of two readings was used in the analyses. Diabetes mellitus was diagnosed if the subject was undergoing treatment with oral hypoglycemic agents or insulin, if the fasting blood glucose (FBG) levels were ≥ 7.1 mmol/l more than twice, or if there was a personal history of diabetes mellitus. These demographic and clinical data were collected from the participants’ medical notes and clerking sheet. A full medication history was obtained from the medical notes. Laboratory results on admission are recorded on the clerking sheet.

Procedures

The patients underwent blood examinations in a fasting state, including routine blood examination, blood glucose, HDLC, low-density lipoprotein cholesterol (LDLC), triglyceride (TG), total cholesterol (TC), homocysteine, and multivariate logistic regression analyses were performed to examine the relationship between HDLC and infarction.

Statistical analyses

Data are expressed in percentages for categorical variables and were compared using the chi-square test. Continuous variables are expressed as means \pm standard deviation (SD) and compared with a Student’s t test for factors with a normal distribution or expressed as median and interquartile range and compared with the Mann-Whitney U test for factors that were not normally distributed. The relationship between HDLC levels and groups of lacunar infarction was evaluated by analysis of variance (ANOVA), LSD test. The independent relationship between different groups and levels of HDLC were assessed using multinomial logistic regression, controlling for comorbidities and demographic characteristics. Multinomial logistic regression analyses were performed to determine whether the serum HDLC levels were independently associated with lacunar infarction after adjustment for the potential confounders. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. All tests of significance were 2-sided. P value < 0.05 was considered statistically significant. All data were analyzed using SPSS (version 19.0, SPSS, Inc., Chicago, IL, USA).

Results

There were 956 consecutive patients aged 50 years and older admitted to the Department of Neurology from August 1, 2013 to August 1, 2014. Finally, 229 patients with obsolete brain infarctions single side (SOBI), 218 with obsolete brain infarctions bilateral sides (BOBI), 193 with both acute stroke

Table 2. HDLC levels in different groups of lacunar infarction by LSD-t.

Groups (I)	Other groups (J)	Mean difference (I-J)	P value	95% CI	
				Lower bound	Upper bound
SOBI	BOBI	-1.00705	.000	-1.1864	-.8277
	AI&SOBI	-.88149	.000	-1.1495	-.6135
	AI&BOBI	-.95883	.000	-1.1780	-.7397
	Control	-.51424	.000	-.6968	-.3317
BOBI	SOBI	1.00705	.000	.8277	1.1864
	AI&SOBI	.12556	.377	-.1561	.4072
	AI&BOBI	.04822	.685	-.1875	.2839
	Control	.49281	.000	.2907	.6949
AI&SOBI	SOBI	.88149	.000	.6135	1.1495
	BOBI	-.12556	.377	-.4072	.1561
	AI&BOBI	-.07733	.619	-.3859	.2312
	Control	.36725	.012	.0835	.6510
AI&BOBI	SOBI	.95883	.000	.7397	1.1780
	BOBI	-.04822	.685	-.2839	.1875
	AI&SOBI	.07733	.619	-.2312	.3859
	Control	.44459	.000	.2064	.6827
Control	SOBI	.51424	.000	.3317	.6968
	BOBI	-.49281	.000	-.6949	-.2907
	AI&SOBI	-.36725	.012	-.6510	-.0835
	AI&BOBI	-.44459	.000	-.6827	-.2064

CI – confidence interval; SOBI – obsolete brain infarctions single side; BOBI – obsolete brain infarctions bilateral sides; AI&SOBI – acute stroke and obsolete lacunar infarctions single side; AI&BOBI – acute stroke and obsolete lacunar infarctions bilateral sides.

and obsolete lacunar infarctions single side (AI&SOBI), 113 with both acute stroke and obsolete lacunar infarctions bilateral sides (AI&BOBI), and 203 without any infarctions (Control) were recruited. Symptoms of lacunar stroke consist of 1 of the recognized lacunar syndromes (pure motor stroke, clumsy hand dysarthria, ataxic hemiparesis, and pure sensory or sensorimotor stroke) in the absence of cortical deficits.

The mean age of the study population was 66.25 years; 52.40% were men. Demographic characteristics of the study population are shown in Table 1. Patients in group BOBI were older ($p<0.05$) and more likely to be male ($p<0.05$) in comparison with the control group. Moreover, patients in group AI&SOBI and AI&BOBI showed significantly higher proportion of hypertension and hyperhomocysteinemia ($p<0.05$; $p<0.01$). We found that patients with recurrent stroke had a younger age of onset and higher frequency of other life-style related diseases such as diabetes and hypertension compared to those without new stroke evidence.

The relationship between HDLC levels and groups of lacunar infarction was evaluated by multiple comparisons (LSD-t) in Table 2. 1) The plasma levels of HDLC in group BOBI, AI&SOBI, and AI&BOBI were higher than in the control group, and were lower in group SOBI than in the control group ($p<0.01$). 2) The plasma levels of HDLC in group AI&SOBI were significantly higher than in group SOBI ($p<0.01$). 3) The plasma levels of HDLC were similar between group AI&SOBI and AI&BOBI.

After adjusting for these factors such as age, sex, TG, TC, LDLC, and history of diabetes, multinomial logistic regression analysis showed that there were significant relationships between HDLC and different lacunar stroke groups ($p=0.001$) (Table 3). In the current study, carried out on middle-aged and elderly subjects, we investigated the associations of HDLC with the presence of LI, and found that patients with lower HDLC levels mostly had obsolete brain infarctions single side. These findings changed when these patients with obsolete brain infarctions single side had a recurrent acute stroke. Further

Table 3. Final model using multinomial logistic regression analysis.

Model	Variables	p value	OR	95% CI	
				Lower bound	Upper bound
SOBI vs. control	HDLC	0.000	0.001	0.002	0.579
BOBI vs. control	HDLC	0.001	64.675	5.331	81.575
AI&SOBI vs. control	HDLC	0.043	22.018	1.107	43.032
AI&BOBI vs. control	HDLC	0.007	42.418	2.764	65.716

OR – odds ratio; CI – confidence interval; SOBI – obsolete brain infarctions single side; BOBI – obsolete brain infarctions bilateral sides; AI&SOBI – acute stroke and obsolete lacunar infarctions single side; AI&BOBI – acute stroke and obsolete lacunar infarctions bilateral sides.

analyses showed that higher HDLC levels were also associated with acute stroke in obsolete brain infarctions bilateral sides. This association was independent of age, sex, and vascular risk factors. We demonstrated that higher HDLC was associated with an increased risk of recurrent acute period of LI. This might provide an adverse perspective of the previously observed association between decreased serum levels of HDLC and stroke in elderly adults.

Variables that correlated with the groups ($p < 0.05$) were included in multinomial logistic regression analysis, which showed that higher HDLC was associated with a greater risk of recurrent LI in the AI&SOBI and AI&BOBI groups. A similar result was observed with the levels of HDLC in group BOBI. By contrast, converse results were observed between group SOBI vs. the Control group.

Discussion

LIs are believed to share similar pathogenic mechanisms; they may be of cardio-embolic origin, or caused by atherosclerotic processes taking place mostly in the small vessel walls and vascular risk factors, such as in advanced age, hypertension [20–22], metabolic syndrome [23,24], and coronary artery disease. Multiple mechanisms of cerebral infarction caused by atherosclerosis have been proposed, including intravascular thrombosis, vascular stenosis, and reduced perfusion pressure in terminal cerebral vessels. In addition, the current study identified that numerous factors – including age, lipoprotein, glycosylated hemoglobin and blood parameters, and diabetes – were correlated with the severity of atherosclerosis, plaque formation, and artery stenosis [15,18,19,25–29].

It appears that the main protective mechanisms of HDLC are reversing cholesterol transport, anti-inflammatory, antioxidant, and, more generally, endothelial protective effects [30–40].

Previous studies inferred that by increasing the concentration of HDLC might achieve favorable effects for stroke [20–22]. A low HDLC is part of the well recognized metabolic syndrome, which is clearly associated with vascular events in Western populations (but whether HDLC has a protective effect on stroke is inconclusive), not to mention in Asian populations who have different dietary habits and HDLC levels. A study by Gu et al. in a Chinese population showed that patients with the CETP-692A/C polymorphism CC genotype had better lipid-regulating effects, exactly opposite to results of a study in Germany [41,42].

Our results mostly suggest that among the Chinese population, HDLC levels are dramatically lower in patients with obsolete brain infarctions single side than in control groups; however, when these patients develop an acute stroke, their HDLC levels are tremendously higher than in control groups. This situation does not occur in patients with obsolete brain infarctions bilateral sides. We infer that the main mechanism of LI single side may be intravascular thrombosis, while the main mechanism of LI bilateral sides may be vascular stenosis and reduced perfusion pressure in terminal cerebral vessels, because atherosclerosis tends to be a systemic vascular system status, with infarctions always scattered and not concentrated on a single side. We found that plasma HDL was independently associated with recurrent LI with obsolete brain infarction single side, suggesting it may be an independent predictor of, as well as a predictive factor for, LI in Chinese people, justifying clinical trials for secondary prevention of stroke by generally increasing HDL level. The difference between single and bilateral side multiple silent lacunar infarcts suggests that higher HDLC levels may increase the risk of intravascular thrombotic infarction but reduce the risk of atherothrombotic infarction in the general Chinese population. In atherothrombotic infarction, we found that the role of HDLC is consistent with findings of previous studies. Additional evidence is needed to support the role of intravascular thrombotic infarction.

Conclusions

The results of the present study indicate that the HDLC plays different roles in acute phase recurrent LI with single/bilateral chronic infarction. These observations provide supporting evidence for developing cerebrovascular disease therapy.

References:

1. Tousignant M, Corriveau H, Kairy D et al: Tai Chi-based exercise program provided via telerehabilitation compared to home visits in a post-stroke population who have returned home without intensive rehabilitation: study protocol for a randomized, non-inferiority clinical trial. *Trials*, 2014; 15: 42
2. Tai W, Kalanithi L, Milstein A: What can be achieved by redesigning stroke care for a value-based world? *Expert Rev Pharmacoecon Outcomes Res*, 2014; 14: 585–87
3. Gallacher KI, Batty G, McLean G et al: Stroke, multimorbidity and polypharmacy in a nationally representative sample of 1,424,378 patients in Scotland: implications for treatment burden. *BMC Med*, 2014; 12: 151
4. Cheng HY, Chair SY, Chau JP: The effectiveness of psychosocial interventions for stroke family caregivers and stroke survivors: a systematic review and meta-analysis. *Patient Educ Couns*, 2014; 95: 30–44
5. Xu B, Liu H, Su N et al: Association between winter season and risk of death from cardiovascular diseases: a study in more than half a million inpatients in Beijing, China. *BMC Cardiovasc Disord*, 2013; 13: 93
6. Wu X, Zhu B, Fu L et al: Prevalence, incidence, and mortality of stroke in the Chinese island populations: a systematic review. *PLoS One*, 2013; 8: e78629
7. Woo J, Lau E, Lam CW et al: Hypertension, lipoprotein(a), and apolipoprotein A-I as risk factors for stroke in the Chinese. *Stroke*, 1991; 22: 203–8
8. Lapergue B, Moreno JA, Dang BQ et al: Protective effect of high-density lipoprotein-based therapy in a model of embolic stroke. *Stroke*, 2010; 41: 1536–42
9. Fuentes B, Martinez-Sanchez P, Diez-Tejedor E: Lipid-lowering drugs in ischemic stroke prevention and their influence on acute stroke outcome. *Cerebrovasc Dis*, 2009; 27(Suppl.1): 126–33
10. Chen Y, Liu Y, Luo C et al: Analysis of multiple factors involved in acute progressive cerebral infarction and extra- and intracranial arterial lesions. *Exp Ther Med*, 2014; 7: 1495–505
11. Chei CL, Yamagishi K, Kitamura A et al: High-density lipoprotein subclasses and risk of stroke and its subtypes in Japanese population: the Circulatory Risk in Communities Study. *Stroke*, 2013; 44: 327–33
12. Amarenco P, Labreuche J, Touboul PJ: High-density lipoprotein-cholesterol and risk of stroke and carotid atherosclerosis: a systematic review. *Atherosclerosis*, 2008; 196: 489–96
13. Imamura T, Doi Y, Ninomiya T et al: Non-high-density lipoprotein cholesterol and the development of coronary heart disease and stroke subtypes in a general Japanese population: the Hisayama Study. *Atherosclerosis*, 2014; 233: 343–48
14. Sarchielli P, Nardi K, Chiasserini D et al: Immunological profile of silent brain infarction and lacunar stroke. *PLoS One*, 2013; 8: e68428
15. Liew G, Baker ML, Wong TY et al: Differing associations of white matter lesions and lacunar infarction with retinal microvascular signs. *Int J Stroke*, 2014; 9: 921–25
16. Del Bene A, Palumbo V, Lamassa M et al: Progressive lacunar stroke: review of mechanisms, prognostic features, and putative treatments. *Int J Stroke*, 2012; 7: 321–29
17. Datta A, Chen CP, Sze SK: Discovery of prognostic biomarker candidates of lacunar infarction by quantitative proteomics of microvesicles enriched plasma. *PLoS One*, 2014; 9: e94663
18. Bailey EL, Smith C, Sudlow CL, Wardlaw JM: Pathology of lacunar ischemic stroke in humans – a systematic review. *Brain Pathol*, 2012; 22: 583–91
19. Arboix A, Blanco-Rojas L, Marti-Vilalta JL: Advancements in understanding the mechanisms of symptomatic lacunar ischemic stroke: translation of knowledge to prevention strategies. *Expert Rev Neurother*, 2014; 14: 261–76
20. Staals J, Makin SD, Doubal FN et al: Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*, 2014; 83: 1228–34
21. Sharma M, Pearce LA, Benavente OR et al: Predictors of mortality in patients with lacunar stroke in the secondary prevention of small subcortical strokes trial. *Stroke*, 2014; 45: 2989–94
22. Altmann M, Thommessen B, Ronning OM et al: Diagnostic accuracy and risk factors of the different lacunar syndromes. *J Stroke Cerebrovasc Dis*, 2014; 23: 2085–90
23. Shah IM, Ghosh SK, Collier A: Stroke presentation in Type 2 diabetes and the metabolic syndrome. *Diabetes Res Clin Pract*, 2008; 79: e1–4
24. Ohta Y, Takao Y, Harada K et al: Metabolic syndrome is a risk factor for acute cerebral infarction in a younger elderly Kurashiki population. *J Stroke Cerebrovasc Dis*, 2012; 21: 231–39
25. Zheng L, Vinters HV, Mack WJ et al: Cerebral atherosclerosis is associated with cystic infarcts and microinfarcts but not Alzheimer pathologic changes. *Stroke*, 2013; 44: 2835–41
26. Sierra C, Coca A, Schiffrin EL: Vascular mechanisms in the pathogenesis of stroke. *Curr Hypertens Rep*, 2011; 13: 200–7
27. Saber Tehrani AS, Kattah JC et al: Small strokes causing severe vertigo: frequency of false-negative MRIs and nonlacunar mechanisms. *Neurology*, 2014; 83: 169–73
28. Khan U, Porteous L, Hassan A, Markus HS: Risk factor profile of cerebral small vessel disease and its subtypes. *J Neurol Neurosurg Psychiatry*, 2007; 78: 702–6
29. Hashimoto Y, Kaneko T, Ohtaki M: [Multiple small subcortical infarction required to distinguish from lacunar infarction: evaluation by use of diffusion-weighted imaging]. *No To Shinkei*, 2003; 55: 1041–46 [in Japanese]
30. Tran-Dinh A, Diallo D, Delbosc S et al: HDL and endothelial protection. *Br J Pharmacol*, 2013; 169: 493–511
31. Savel J, Lafitte M, Pucheu Y et al: Very low levels of HDL cholesterol and atherosclerosis, a variable relationship – a review of LCAT deficiency. *Vasc Health Risk Manag*, 2012; 8: 357–61
32. Rodriguez-Sanz A, Fuentes B, Martinez-Sanchez P et al: High-density lipoprotein: a novel marker for risk of in-hospital infection in acute ischemic stroke patients? *Cerebrovasc Dis*, 2013; 35: 291–97
33. Merle BM, Maubaret C, Korobelnik JF et al: Association of HDL-related *loci* with age-related macular degeneration and plasma lutein and zeaxanthin: the Alienor study. *PLoS One*, 2013; 8: e79848
34. Mehta NN, Gelfand JM: High-density lipoprotein cholesterol function improves after successful treatment of psoriasis: a step forward in the right direction. *J Invest Dermatol*, 2014; 134: 592–95
35. Lehti M, Donelan E, Abplanalp W et al: High-density lipoprotein maintains skeletal muscle function by modulating cellular respiration in mice. *Circulation*, 2013; 128: 2364–71
36. Knolle P, Kneilling M, Rocken M et al: Controlling for apolipoprotein A-I concentrations changes the inverse direction of the relationship between high HDL-C concentration and a measure of pre-clinical atherosclerosis. *Nat Immunol*, 2013; 231: 181–86
37. He L, Qin S, Dang L et al: Psoriasis decreases the anti-oxidation and anti-inflammation properties of high-density lipoprotein. *Biochim Biophys Acta*, 2014; 1841(12): 1709–15
38. Guo L, Ai J, Zheng Z et al: High density lipoprotein protects against polymicrobe-induced sepsis in mice. *J Biol Chem*, 2013; 288: 17947–53
39. De Nardo D, Labzin LI, Kono H et al: High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. *Nat Immunol*, 2014; 15: 152–60
40. Badeau RM, Metso J, Kovanen PT et al: The impact of gender and serum estradiol levels on HDL-mediated reverse cholesterol transport. *Eur J Clin Invest*, 2013; 43: 317–23

The strengths of this study included the consecutive study design with a relatively large sample size, multiple groups, and comparisons of different patterns. However, this study also had limitations in that it was not based on the general population, and the results may be influenced by the limited representativeness of the sample selected from hospitalized patients.

41. Gu GL, Xu XL, Yang QY, Zeng RL: Effect of CETP polymorphism on atorvastatin lipid-regulating effect and clinical prognosis of patients with coronary heart disease. *Med Sci Monit*, 2014; 20: 2824–29
42. Blankenberg S, Rupprecht HJ, Bickel C et al: Common genetic variation of the cholesteryl ester transfer protein gene strongly predicts future cardiovascular death in patients with coronary artery disease. *J Am Coll Cardiol*, 2003; 41: 1983–89