Study of plasma levels of ApoA-I and ApoB for prognosis of acute ischemic stroke

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Abstract

Background. The levels of plasma ApoA-I, ApoB and the ratio of ApoA-I/ApoB were reported as risk factors of stroke. However, if they are prognostic factors of stroke is still unknown. This article is to demonstrate the Study of plasma levels of ApoA-I and ApoB levels for prognosis of acute ischemic stroke. *Method*. From Aug 24th 2005 to Apr 25th 2007, patients with acute ischemic stroke (AIS) came to Henan Stroke Registry Centre in the First Affiliated Hospital of Zhengzhou University were voluntarily enrolled to this study. Parameters related to prognosis of AIS of these patients were tested at admission counter, such as Plasma ApoA-I, ApoB, NIHSS, age, gender. Parameters for patients' self-care ability, such as Modified Rankin Scale (MRS), Barthel Index (BI) were collected one month later. We established MRS < 3 or BI > 60 as patient independence. Then, we used Logistic regression to detect independent predictors for the prognosis of AIS. *Results*. During the 2 years study, we collected 248 patients in all. Of these patients, ApoA-I ranged from 0.20 g/L to 2.30 g/L, and average level was 1.04 ± 0.29 g/L; ApoB ranged from 0.40 g/L to 2.40 g/L, and average level was 0.91 ± 0.32 g/L; ApoA-I/ApoB ratio ranged from 0.21 to 5.50, and its median was 1.17. MRS < 3 was observed in 69% (171/248) of the patients at 1 month follow-up, and BI > 60 in 69.6% (172/248) of the patients. Multivariate analysis showed ApoA-I/ApoB independently associated with MRS score (OR = 0.46, 95%CI = 0.213 – 0.977, $P = 0.043$) and BI score (OR = 0.45, 95%CI = 0.208 – 0.966, $P = 0.040$). *Conclusions*. Our results indicated that ApoA-I/ApoB ratio in AIS patients was independently associated with one month MRS score and BI score. Higher the ApoA-I/ApoB ratio, better the recovery outcome patients would achieve. High ApoA-I/ApoB ratio could be a predictor for good prognosis of AIS. [Life Science Journal. 2009; 6(2): 88 – 92] (ISSN: 1097 – 8135).

Keywords:

1 Introduction

Stroke is the third leading cause of all disease deaths as well as the first leading cause of severe disability in both developing and developed countries[1]. Finding out predictors for stroke outcome, and interfering in them will improve patients' recovery, and reduce the risk of life threat. Some modifiable predictors, such as blood glucose, blood pressure, and plasma lipids are being studied. So far, hyperglycemia in acute phase has been regarded as a predictor of bad prognosis of stroke[2], and very high or very low, or fluctuating blood pressure in acute phase has also been considered bringing poor outcome. However, the relationship between plasma lipids, lipoproteins and apolipoproteins (Apos) in acute phase and stroke is still not sure. Researches on the relationship of plasma lipids and prognosis of stroke are few and mainly focused on cholesterol, and results always conflict with each other. Some authors' findings suggested that higher levels of cholesterol were associated with a better outcome in the early phase after ischemic stroke[8]; more researchers induced contradictory conclusions[9–11]. In addition, these trials were all retrospective in design. Therefore, it's necessary to study other lipid sub-fractions and stroke using prospective method.

Clinical trails showed statins reduced the risk of ischemic stroke and coronary heart disease nearly to the same

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extend. Scandinavian Simvastatin Survival Study (4S)[3] indicated Simvastatin reduced the risk of stroke by 36%; Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study[4] demonstrated that Pravastatin reduced the risk of stroke by 19%, and non-hemorrhagic stroke by 23%. Weak associations between total and low density lipoprotein (LDL) cholesterol and ischemic stroke compared with coronary heart disease (CHD) are at odds with the similar effectiveness of statin drugs in preventing ischemic stroke and CHD, suggesting that other lipid sub-fractions that are affected by statins might be better predictors of ischemic stroke. Plasma ApoA-I, ApoB levels and ApoA-I/ApoB ratio are lipid sub-fractions affected by statins.

Some studies found ApoA-I/ApoB ratio was significantly associated with the occurrence of stroke. AMORIS prospective study[5] linked the ApoB/ApoA-I ratio to the risk of fatal stroke in a similar fashion as myocardial infarction and other ischemic events. Adnan I. Qureshi *et al*[6] reported the ApoA-I/ApoB ratio was inversely associated with both myocardial infarction and stroke and might be an important protective clinical marker for atherosclerosis. A prospective cohort study[7] which enrolled 261 patients with previous TIA and followed up for 10 years found that ApoB and the ApoB/ApoA-I ratio were predictive of ischemic stroke in patients with previous TIA. However, these studies are about ApoA-I, ApoB levels and ApoA-I/ApoB ratio and stroke risk, not stroke outcome. We conducted a small prospective cohort study to investigate plasma ApoA-I, ApoB levels, ApoA-I/ApoB ratio and early outcome of acute ischemic stroke (AIS), aiming at searching for a new predictor of prognosis of AIS.

2 Subjects and Methods

2.1 Subjects

2.1.1 Resources of Subjects. From Aug 24th 2005 to Apr 25th 2007, patients with AIS came to Henan Stroke Registry Centre in the First Affiliated Hospital of Zhengzhou University were voluntarily enrolled to this study.

2.1.2 Diagnostic criteria. 1) The diagnostic criteria for stroke is: Acute onset, focal neurological impairments (some with comprehensive neurological impairments), with signs and symptoms lasting more than 24 hours (or patient die within 24 hours) or rapidly vanishing symptoms with imaging of an acute clinically relevant brain lesion in patients. Exclude non-vascular causes[12]; 2) Exclude hemorrhage by the first time computerized tomography (CT)/magnetic resonance imaging (MRI).

2.1.3 Inclusion criteria. 1) In accordance with the diagnostic criteria above; 2) At any age; 3) Within 15 days since symptoms onset; 4) First stroke, or recurrent stroke with no neurological impairments before onset.

2.2.4 Exclusion criteria. 1) Patients with comorbid hematological diseases or severe renal failure or hepatic failure; 2) Dependence caused by any reason before onset; 3) Inability to give informed consent.

2.2 Methods

2.2.1 Study design. Prognostic study.

2.2.2 Sample size estimation. Empirical formula for sample size estimation of multivariate analysis: sample size = variable number × (5 – 10).

2.2.3 Cases collection. Cases collection included 4 steps: 1) When informed consent got, residents filled out standard stroke registry form for each patient. The form contained patients' age, gender, time from onset to admission, past history, alcohol consumption, smoking status, height, weight, abdomen circumference; first blood pressure on admission, blood chemistry parameters on admission including hemoglobin (HGB), platelets (PLT), hematocrit (HCT), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), international normalized ratio (INR), blood urea nitrogen (BUN), creatinine, fasting serum glucose, triglyceride (TG), cholesterol (CHO), LDL, high density lipoprotein (HDL), ApoA-I, ApoB; color ultrasound of carotid artery and heart, brain CT/MRI, transcranial doppler sonography (TCD), Infarction subtype, medications given, rehabilitation care taken, complications and discharge diagnosis. All blood chemistry test were done in the hospital central chemistry lab. Infarction subtype was classified according to Oxford Community Stroke Project (OCSP) stroke classification: total anterior circulation infarction (TACI), partial anterior circulation infarction (PACI), lacunar infarction (LACI), posterior circulation infarction (POCI); 2) Patients' consciousness and neurological impairments were assessed immediately by trained residents using GCS (Glasgow Coma Scale), SSS (Scandinavian Stroke Scale) and NIHSS (National Institute of Health Stroke Scale); 3) On day30 ± 3 after onset, patients received phone calls from residents who didn' participate step 1) and step 2) work. Through telephone, residents evaluated patients' self-care ability using modified Rankin Scale (MRS) and Barthel Index (BI) and recorded the scores; 4) All information collected were saved in SPSS13.0.

2.2.4 Determination of factors probably affecting prognosis of AIS. After checking related studies, we

chose age, gender, infarction subtypes, severity of early neurological impairments (which is evaluated by NIHSS), time from onset to admission, fasting glucose on admission, total cholesterol, plasma ApoA-I, ApoB levels and ApoA-I/ApoB ratio as probable predictors for prognosis of AIS, in accordance with common agreements. These data were all recorded in stroke registry forms, and they were defined as independent variables in statistic analysis. Then, we chose patients' MRS and BI scores at 1 month follow-up as the end point, and they were defined as independent variables in statistic analysis. According to common agreements and related researches, we defined MRS < 3 or BI > 60 as patient independence, MRS ≥ 3 or BI ≤ 60 as dependence, and MRS = 5 and/or BI = 0 is for death.

2.3 Statistical analysis

Analyzing data with SPSS13.0.

Independent variables and dependent variables are shown in Table 1.

3 Results

3.1 General profiles

248 AIS patients documented by CT or MRI were enrolled, and none missed the 1month follow-up. Table 2 and Table 3 demonstrate general data of the patients.

3.2 Relationship between ApoA-I, ApoB, ApoA-I/ApoB and prognosis of AIS

3.2.1 With MRS. We defined gender, age, time from symptom onset to admission, infarction subtype, NIHSS on admission, fasting blood glucose on admission, total cholesterol on admission, ApoA-I, ApoB and ApoA-I/ApoB on admission as concomitant variables, and MRS at 1 month follow up as dependent variable. Then we used multivariate logistic regression analyzing the data. Results showed that ApoA-I/ApoB was significantly associated with MRS (P = 0.042, OR = 0.42, 95%CI (0.182, 0.969)). Every 1 unit increase in ApoA-I/ApoB was associated with 0.42 times reduction in risk of patient dependence at one month (MRS ≥ 3). Other variables associated with one month MRS were age, infarction subtype, NIHSS on admission. However, sex, time from symptom onset to therapy, ApoA-I, ApoB, fasting blood glucose, total cholesterol on admission were not associated with one month MRS (Table 4).

3.2.2 With BI. In this part, BI was defined as dependent variable. Then we used multivariate logisticl regression analyzing the data. Results showed that the ApoA-I/ApoB was significantly associated with BI (P = 0.046, OR = 0.425, 95%CI (0.184, 0.983)). Every 1 unit increase in ApoA-I/ApoB was associated with 0.425 times reduction in risk of poor outcome after one month (MRS ≥ 3). Other variables associated with BI were age, infarction subtype, NIHSS on admission. However, sex, time from symptom onset to therapy, ApoA-I, ApoB, fasting blood glucose, total cholesterol on admission were not associated with BI (Table 5).

Table 2. Categorical variables

	n	%
Male	146	58.9
Female	102	41.1
Urban	160	64.5
Rural	88	35.5
Hypertension	146	58.9
Diabetes	53	21.4
Hyperlipoidimia	46	18.5
TIA	30	12.1
Migraine	11	4.4
Smoke	87	35.1
Alcohol	63	25.4
Previous stroke	60	24.2
TACI	8	3.2
PACI	72	29.0
LACI	121	48.8
POCI	47	19.0
MRS < 3	171	69.0
3 ≤ MRS < 5	77	31.0
BI > 60	79	69.3
0 < BI ≤ 60	77	30.7
MRS = 5 and BI = 0	7	2.8

Table 3. Ccontinuous variables

variable	Sum total	Minimal value	Maximal value	Mean ± SD
Age	248	23	93	62.46 ± 12.71
Time form symptom onset to admission	248	0.1	360.0	7.5
NIHSS on admission	248	1	56	4
FBG on admission	248	3.26	17.58	5.39
TC on admission	248	2.38	11.95	5.09 ± 1.26
ApoA-I on admission	248	0.20	.30	1.04 ± 0.29
ApoB on admission	248	0.40	2.40	0.91 ± 0.32
ApoA-I/ApoB	248	0.21	5.50	1.17

Table 4. Results of Logistic regression analysis 1

	B	SE	Wald	Sig	Exp (B)	95%CI for EXP(B)	
						Lower	Upper
Age	0.050	0.016	9.347	0.002*	1.051	1.018	1.086
Infarction subtypes			12.888	0.005*			
NIHSS on admission	0.234	0.044	27.747	0.000*	1.263	1.158	1.378
ApoA-I/ApoB	– 0.867	0.426	4.137	0.042*	0.420	0.182	0.969
Sex				0.387			
Time from symptom onset to treatment				0.421			
FBG on admission				0.099			
TC on admission				0.395			
ApoA-I on admission				0.318			
ApoA-I on admission				0.980			

B = LnOR, Wald = Walds test value, OR = odds ratio, 95%CI Lower = 95% lower limit of confidence interval, Upper = 95% upper limit of confidence interval. $P < 0.05$ and 95%CI $\neq 1$ had statistical significance, Sig = *P* value.

Table 5. Results of Logistic regression analysis 2

	B	SE	Wald	Sig	Exp (B)	95%CI for EXP(B)	
						Lower	Upper
Age	0.059	0.017	12.146	0.000*	1.060	1.026	1.096
Infarction subtypes			12.443	0.006*			
NIHSS on admission	0.226	0.044	26.843	0.000*	1.254	1.151	1.366
ApoA-I/ApoB	– 0.855	0.428	3.996	0.046*	0.425	0.184	0.983
Gender				0.352			
Time from symptom onset to treatment				0.312			
FBG on admission				0.080			
TC on admission				0.318			
ApoA-I on admission				0.493			
ApoA-I on admission				0.519			

B = LnOR, Wald = Walds test value, OR = odds ratio, 95%CI Lower = 95% lower limit of confidence interval, Upper = 95% upper limit of confidence interval. $P < 0.05$ and 95%CI $\neq 1$ had statistical significance, Sig = *P* value.

4 Discussion

4.1 The function of Apos in lipids metabolism

Basic researches reveal that Apos plays important roles in lipids metabolism. ApoA-I is the major Apo in HDL, and it is probably important in protecting against premature atherosclerosis. Genetic defects that cause the inability to synthesize ApoA-I cause very low plasma concentrations of HDL cholesterol and premature coronary artery disease in the fourth and fifth decades[13–16]. Conversely, an increased rate of ApoA-I production causes high plasma levels of HDL cholesterol and may be associated with protection from premature coronary artery disease based on familial longevity[17]. Furthermore, overexpression of human ApoA-I in transgenic mice inhibits the development of atherosclerosis[18]. ApoB is the major Apo in chylomicrons, VLDL, intermediate-density lipoprotein, and LDL. It is an essential structural part in these lipoprotein particles. For example, the genetic inability to secrete ApoB causes the absence of these lipoproteins in plasma[19]. Furthermore, mutations in the ApoB gene can cause low levels of ApoB and LDL cholesterol and may be associated with protection from premature coronary artery disease[20]. In addition, ApoB acts as a ligand for the LDL receptor, mediating the cellular uptake and degradation of LDL[21]. Only one

molecule of ApoB exists per lipoprotein particle, and thus the quantity of ApoB in fasting plasma is a measure of the number of LDL and VLDL particles. In fact, the plasma levels of "non-HDL cholesterol", which includes both LDL and VLDL, are correlated with plasma ApoB levels[22,23]. However, in contrast to the constant 1 : 1 molar ratio of ApoB per LDL and VLDL particle, the amount of cholesterol in these lipoproteins varies widely. Therefore, plasma ApoB levels may be a better assay of the concentration of atherogenic lipoprotein particles than are LDL cholesterol or non-HDL cholesterol levels[24,25].

4.2 The association between ApoA-I/ApoB and outcome of AIS

Avogaro *et al*[26] considered Apos better discriminators than lipids for atherosclerosis. AMORIS[5] study found no significant relevance between ApoA-I, ApoB and risk of stroke. A community-based cohort study in Taiwan-Chin-Shan Community Cardiovascular Study[27], as one of the few studies on plasma ApoA-I, ApoB and stroke in Chinese people, reported ApoA-I but not ApoB levels might serve as an effect modifier of hypertension for the risk of stroke events. However, these studies were all about stroke risk, and no article on plasma levels of ApoA-I, ApoB, ApoA-I/ApoB and prognosis of AIS has been published yet. This study found no significant relevance between plasma ApoA-I, ApoB levels and short-time outcome of AIS, with no contradiction with previous researches on plasma ApoA-I, ApoB levels and risk of AIS.

More and more concerns has been attracted by ApoA-I/ApoB ratio, a novel predictor for high risk of atherosclerosis. A study[28] showed high ApoB and a high ApoB/ApoA-I ratio were strongly related to increased coronary risk, while high ApoA-I was inversely related to risk. Walldius and Jungner[29] reviewed articles recently published on ApoB/ApoA-I ratio and risk of atherosclerosis and concluded that the cholesterol balance determined as the ApoB/ApoA-I ratio has repeatedly been shown to be a better marker than lipids, lipoproteins and lipid ratios. In all, results indicated that the ApoB/ApoA-I ratio was a simple, accurate and new risk factor for CV disease – the lower the ApoB/ApoA-I ratio, the lower the risk. As a prognostic study, this research showed higher ApoA-I/ApoB ratio was associated with better outcome at 1 month follow-up, suggesting a potential protective role higher ApoA-I/ApoB played in the neurofunction recovery post stroke.

Mechanism of neuroprotective function of higher ApoA-I/ApoB ratio probably lies in the fact that ApoB/ApoA-I ratio is a better marker than lipids, lipoproteins and lipid ratios to evaluate the balance of atherogenic and antiatherogenic lipoproteins. Antiatherogenic lipoprotein HDL activities include endothelium protection, anti-inflammation, anticoagulation, antioxidation, as well as diminishing brain injury by inhibiting inflammation, oxidative stress post-stroke[30–33]. In addition, HDL, mainly ApoA-I, increases the resistance of endothelial cells against oxidized LDL and prevents its toxic (apoptotic) effect by blocking the pathogenic intracellular signaling (culminating in sustained Ca^{2+} rise) involved in cell death[34].

4.3 Other factors and outcome of AIS

The relationship between lipids and stroke is not clear yet. Some large sample prospective study found the elevation of plasma lipids, including TG, CHO, and LDL were not able to predict the occurrence of stroke[35–38]. Some authors' findings suggested that higher levels of cholesterol were associated with a better outcome in the early phase after ischemic stroke8; more researchers induced contradictory conclusions[9–11]. This study showed no significant association between CHO and short-time outcome of AIS, in accordance with most similar researches.

Unlike previous studies, this study didn't conclude that fasting glucose on admission was relevant to outcome of AIS. The possible reason is that glucose fluctuates frequently in the superacute phase of AIS. Previous researches on glucose and stroke enrolled patients who admitted to hospital mainly within 3 days since onset; this study enrolled patients admitted to hospital within 15 days, whose glucose levels couldn't represent the level in the superacute phase.

5 Conclusions

ApoA-I/ApoB ratio is significantly associated with short-time prognosis of AIS. Higher ApoA-I/ApoB ratio might be a predictor of good outcome of AIS. As this is a small-sample pilot study, further large sample researches are needed.

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