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Acute and Long-term Changes in Serum Lipids After Acute Stroke

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We studied serum lipid profiles in 171 patients ≤48 hours after the onset of acute stroke and 3 months later. The 83 patients suffering cerebral infarction had significantly higher serum concentrations of total cholesterol, low density lipoprotein-cholesterol, and apolipoprotein B and significantly lower serum concentrations of triglycerides and lipoprotein (a) ≤48 hours after ictus than 3 months later. The lipid profiles of the 53 patients suffering lacunar infarction were similar on both occasions, the only significant differences being higher total cholesterol and low density lipoprotein-cholesterol concentrations ≤48 hours after ictus. No significant changes were observed among the 35 patients suffering cerebral hemorrhage apart from a significantly higher concentration of high density lipoprotein$_3$-cholesterol ≤48 hours after ictus. Our study, with many patients classified according to stroke subtype, gives results different from those of previous studies with much fewer patients. We conclude that in studies of serum lipid and lipoprotein concentrations as risk factors for cerebral infarction, comparing values obtained ≤48 hours after admission with control values may incorrectly identify certain lipid fractions as risk factors. (*Stroke* 1990;21:1407–1411)

In the investigation of serum concentrations of lipids, lipoproteins, and apolipoproteins as risk factors for stroke, it is unclear whether the acute stroke affects the serum lipid profile or at what stage after ictus serum lipid values can be effectively compared with those from control subjects. It is also important to examine lipid profiles in patients with different stroke subtypes separately since different subtypes may have different risk factors. In two previous studies, few patients (26[1] and 22[2]) were examined, not all subtypes of stroke were defined, only men were considered in one,[2] and conflicting results were obtained. Also, there was no information given on temporal changes in the concentrations of apolipoprotein fractions or lipoprotein (a) after acute stroke, which is of particular interest since apolipoproteins may be better indicators of atherosclerosis than lipids,[3] and since lipoprotein (a) appears to be a strong indicator for cerebrovascular disease.[4] We examined the lipid profiles of patients with acute stroke classified into stroke subtypes ≤48 hours after ictus and repeated the profile 3 months later to determine what effect, if any, the acute stroke had on the serum lipid profile.

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Subjects and Methods

We studied 304 consecutive patients with acute stroke admitted to a general district hospital between January and June of 1989. All patients were examined by a neurologist ≤24 hours after admission and were classified as suffering one of three stroke subtypes (cerebral infarction, lacunar infarction, or intracerebral hemorrhage) based on the clinical examination and computed tomography (CT) or autopsy if the patient died before CT could be performed. Cerebral infarction was diagnosed if neurologic deficits were accompanied by a hypodense lesion >15 mm in diameter in an appropriate area on a cranial CT scan. Lacunar infarction was diagnosed if the patient presented with a pure motor stroke, a pure sensory stroke, ataxic hemiparesis, or a sensorimotor stroke in the absence of a visual field defect and evidence of higher cerebral dysfunction[5] and a hypodense lesion ≤15 mm in diameter or a normal CT scan. A Glasgow Coma Scale score was obtained for each patient. Subjects with liver disease, renal failure, or thyroid disease were excluded. Forty-eight patients had a history of diabetes mellitus or were receiving insulin or oral hypoglycemic drugs.

TABLE 1. Demographic and Clinical Information for Stroke Patients on Admission and at 3-Month Follow-up

	At admission (n=304)	At follow-up (n=171)
Age (mean±SD years)	70.2±11.4	68.3 ±11.2
Sex		
Male	157	89
Female	147	82
Stroke subtype		
Cerebral infarction	143 (36)	83
Lacunar infarction	75 (8)	53
Intracerebral hemorrhage	.86 (37)	35
Diabetes mellitus	48 (11)	29

Numbers in parentheses, patients who died by 3 months.

We obtained 20 ml venous blood after a ≥12-hour fast and ≤48 hours after the onset of stroke for routine blood tests as well as for a lipid profile. Serum was stored at −70° C for batch assay of the serum concentrations of total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol and subfractions (HDL-C, HDL_2-C, and HDL_3-C), low density lipoprotein (LDL) cholesterol and subfraction (LDL-C and very low density lipoprotein [VLDL]-C), apolipoproteins A_1 and B (Apo A_1 and Apo B), and lipoprotein (a). The concentrations of cholesterol and triglycerides were assayed enzymatically using commercial reagents (Baker Instruments Corp., Allentown, Pa.), and the concentrations of HDL-C, HDL_2-C, and HDL_3-C were determined after fractional precipitation with dextran sulfate-$MgCl_2$.[6] We calculated the concentrations of LDL-C and VLDL-C using the formula of Friedewald et al,[7] and we assayed the concentrations of Apo A_1 and Apo B by rate immunonephelometry (array analyzer, Beckman Instruments, Inc., Bera, Calif.). Lipoprotein (a) concentration was measured by immunoradiometric assay (Pharmacia Diagnostic AB, Uppsala, Sweden). Results for all assays were not available for all patients. The interassay coefficient of variation for cholesterol was 1.9% at 6.4 mmol/l, that for triglycerides was 2.6% at 1.9 mmol/l, that for HDL-C was 5.4% at 0.86 mmol/l, that for Apo A_1 was 2.2% at 136 mg/dl, that for Apo B was 2.8% at 85 mg/dl, and that for lipoprotein (a) was 5.3% at 52 mg/dl.

We recalled all surviving patients to the hospital 3 months later for a repeat blood test after a 12-hour (overnight) fast. No patient had been placed on a special diet or given any drugs to lower lipid levels.

Results were analyzed using the Statistical Package for the Social Sciences on an IBM personal

TABLE 2. Lipid Profile in 171 Patients ≤48 Hours and 3 Months After Acute Stroke by Subtype

	All strokes			Cerebral infarction			Lacunar infarction			Intracerebral hemorrhage		
Lipid	n	≤48 hr after ictus	3 mo later	n	≤48 hr after ictus	3 mo later	n	≤48 hr after ictus	3 mo later	n	≤48 hr after ictus	3 mo later
Cholesterol												
mmol/l	171	5.7±1.2*	5.3±1.3	83	5.9±1.3‡	5.4±1.4	53	5.6±1.1†	5.3±1.0	35	5.5±1.1	5.2±1.4
mg/dl		221±46	205±50		228±50	209±54		217±43	205±39		213±43	201±54
Triglycerides												
mmol/l	169	1.5±0.8†	1.7±1.0	83	1.5±0.9†	1.8±1.1	52	1.5±0.9	1.6±0.9	34	1.6±0.8	1.7±0.8
mg/dl		133±71	151±89		133±80	159±97		133±80	142±80		142±71	151±71
HDL-cholesterol												
mmol/l	167	1.2±0.4	1.2±0.3	81	1.2±0.4	1.2±0.3	52	1.2±0.4	1.2±0.3	34	1.3±0.5	1.1±0.4
mg/dl		46±15	46±12		46±15	46±12		46±15	46±12		50±19	43±15
HDL_2-cholesterol												
mmol/l	166	0.4±0.3	0.4±0.3	81	0.4±0.3	0.4±0.3	51	0.4±0.3	0.4±0.3	34	0.4±0.4	0.4±0.3
mg/dl		15±15	15±15		15±15	15±15		15±15	15±15		15±15	15±15
HDL_3-cholesterol												
mmol/l	167	0.8±0.2†	0.7±0.2	81	0.8±0.2	0.7±0.2	52	0.8±0.2	0.8±0.2	34	0.9±0.3†	0.7±0.2
mg/dl		31±8	27±8		31±8	27±8		31±8	31±8		35±12	27±8
LDL-cholesterol												
mmol/l	167	3.8±1.1‡	3.5±1.2	82	4.0±1.1‡	3.5±1.2	51	3.7±1.0†	3.3±0.9	34	3.6±1.0	3.6±1.6
mg/dl		147±43	135±46		155±43	135±46		143±39	128±35		139±39	139±62
VLDL-cholesterol												
mmol/l	167	0.7±0.4	0.8±0.4	82	0.7±0.5	0.8±0.5	51	0.7±0.4	0.7±0.4	34	0.7±0.4	0.8±0.4
mg/dl		27±15	31±15		27±19	31±19		27±15	27±15		27±15	31±15
Apo A_1 (mg/dl)	161	122.0±30.9	117.4±26.4	78	121.2±31.8	115.6±26.4	49	119.1±26.8	119.9±23.8	34	127.5±34.7	117.2±29.8
Apo B (mg/dl)	163	95.6±27.9*	87.1±23.4	79	98.0±26.5‡	89.5±24.7	49	90.5±25.3	83.9±22.2	35	98.7±32.9	86.9±23.4
Lipoprotein (a) (mg/dl)	164	38.8±32.6†	43.7±36.8	81	39.7±28.8†	46.5±39.5	49	38.1±36.8	41.6±35.2	34	32.7±32.1	34.2±30.0

HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein; Apo, apolipoprotein. Data are mean±SD.

*†‡p<0.0001, 0.05, 0.001, respectively, different from 3-month value by paired t test and Wilcoxon's rank sum test.

TABLE 3. Lipid Profile in Patients ≤48 Hours After Acute Stroke by Severity and Outcome

	Severity				Outcome			
	≥10		<10		Alive		Died	
Lipid	*n*	Mean±SD	*n*	Mean±SD	*n*	Mean±SD	*n*	Mean±SD
Cholesterol								
mmol/l	223	5.7±1.3	68	5.1±1.4*	210	5.8±1.2	81	5.2±1.4*
mg/dl		221±50		197±54		224±46		201±54
Triglycerides								
mmol/l	222	1.5±0.9	68	1.3±0.9	209	1.5±0.8	81	1.3±1.0
mg/dl		133±80		115±80		133±71		115±89
HDL-cholesterol								
mmol/l	221	1.2±0.4	67	1.3±0.5	207	1.2±0.4	81	1.3±0.5
mg/dl		46±15		50±19		46±15		50±19
HDL_2-cholesterol								
mmol/l	221	0.4±0.3	67	0.5±0.3	207	0.4±0.3	81	0.5±0.4
mg/dl		15±12		19±12		15±12		19±15
HDL_3-cholesterol								
mmol/l	221	0.8±0.2	67	0.8±0.3	207	0.8±0.2	81	0.8±0.2
mg/dl		31±8		31±12		31±8		31±8
LDL-cholesterol								
mmol/l	221	3.8±1.1	68	3.3±1.2*	208	3.8±1.1	81	3.4±1.2‡
mg/dl		147±43		128±46		147±43		132±46
VLDL-cholesterol								
mmol/l	220	0.7±0.4	68	0.6±0.3†	207	0.7±0.4	81	0.6±0.3‡
mg/dl		27±15		23±12		27±15		23±12
Apo A_1 (mg/dl)	214	122.9±31.7	68	119.8±41.5	201	122.0±31.7	81	122.0±40.0
Apo B (mg/dl)	215	93.6±26.4	68	83.0±34.6‡	202	94.7±28.5	81	82.6±28.4†
Lipoprotein (a) (mg/dl)	216	37.7±31.4	68	35.0±35.0	203	38.2±32.5	81	34.2±31.9

Severity as score on Glasgow Coma Scale. HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein; Apo, apolipoprotein.

*†‡$p<0.001$, 0.05, 0.01, respectively, different from respective subgroup by Kruskal-Wallis one-way analysis of variance.

computer. We used Student's paired *t* test and Wilcoxon's rank sum test to detect significant differences between lipid profiles ≤48 hours after ictus and 3 months later. We used the Kruskal-Wallis analysis of variance to compare lipid profiles by stroke severity and outcome. We used discriminant function analysis to examine the contribution of lipid values after acute stroke in predicting mortality.

Results

Of the 304 patients (157 men and 147 women), a repeat blood sample was obtained in 171 (89 men and 82 women) (Table 1). Of the remaining 133 patients, no repeat blood sample was obtained in 108 (81 had died by 3 months, nine had moved from Hong Kong, seven could not be traced because they had moved, six refused to attend the follow-up, and five were in other hospitals) and in 25, either the first or the second blood samples were misplaced and could not be used for comparison.

For all strokes, concentrations of cholesterol, HDL_3-C, LDL-C, and Apo B were significantly higher while those of triglycerides and lipoprotein (a) were significantly lower ≤48 hours after ictus than at 3 months (Table 2). Most of these differences were also present in patients with cerebral infarction and, to a lesser extent, in those with lacunar infarction. The only significant difference in lipid profiles among patients with intracerebral hemorrhage was an HDL_3-C concentration significantly higher ≤48 hours after ictus than at 3 months.

Since these differences may be related to severity of the stroke, we analyzed the lipid profiles ≤48 hours after ictus according to severity (as indicated by the Glasgow Coma Scale score) and outcome (Table 3). Patients with a score of <10 and those who died had significantly lower cholesterol, LDL-C, VLDL-C, and Apo B concentrations. The Glasgow Coma Scale score (not shown) correlated significantly with concentrations of cholesterol and LDL-C ($r=0.24$, $p<0.001$, $n=291$), VLDL-C ($r=0.16$, $p<0.01$, $n=288$), and Apo B ($r=2.3$, $p<0.001$, $n=283$).

Discriminant function analysis selected age, Glasgow Coma Scale score, loss of consciousness on presentation, speech deficit, admission glucose concentration, and VLDL-C concentration as contributing to the prediction of mortality. Mortality was accurately predicted in 67% of our patients. If VLDL-C concentration was omitted from the function, the accuracy was 64%. Therefore, serum lipid

TABLE 4. Lipid Profile in 304 Age- and Sex-Matched Subjects Without Stroke

Lipid	Mean±SD
Cholesterol	
mmol/l	5.46±1.14
mg/dl	211±44
Triglycerides	
mmol/l	1.58±1.17
mg/dl	140±104
HDL-cholesterol	
mmol/l	1.34±0.42
mg/dl	52±16
HDL_2-cholesterol	
mmol/l	0.53±0.35
mg/dl	32±14
HDL_3-cholesterol	
mmol/l	0.83±0.27
mg/dl	32±10
LDL-cholesterol	
mmol/l	3.32±1.25
mg/dl	128±48
VLDL-cholesterol	
mmol/l	0.7±0.54
mg/dl	27±21
Apo A_1 (mg/dl)	131.3±29.3
Apo B (mg/dl)	84.8±24.1
Lipoprotein (a) (mg/dl)	21.1±27.0

HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein; Apo, apolipoprotein.

concentrations contributed little to the prediction of mortality after acute stroke.

The lipid profile of 304 apparently healthy subjects without stroke living in the community is provided for comparison (Table 4). The healthy subjects were matched for age and sex with the stroke patients. Cholesterol, LDL-C, and Apo B concentrations in the stroke patients 3 months after ictus were similar to those of the healthy subjects. Detailed analysis of the differences in lipid profiles between the stroke patients and the healthy subjects will be reported elsewhere as a case–control study of stroke risk factors for Chinese subjects.

Discussion

Our results differ from those of previous studies addressing this issue. In a study of 26 patients, Hollanders and Shafar[1] found that serum cholesterol concentration fell progressively after acute stroke but by 3 months returned to levels comparable to those 48 hours after ictus. However, the number of subjects was small, the acute stroke syndrome was not classified as to subtype, and HDL-C, apolipoprotein, and lipoprotein (a) concentrations were not determined. In a more recent study assessing temporal changes in serum total cholesterol, triglyceride, LDL-C, VLDL-C, and HDL-C concentrations, only 22 men with cerebral infarction or transient ischemic attacks were studied.[2] No information was available for other stroke subtypes, for the apolipoprotein fractions or lipoprotein (a), or for women. Serum cholesterol and triglyceride concentrations were found to be depressed initially, but at 3 months both values were higher. Both studies seem to indicate a lipid-lowering effect of acute stroke, similar to the decrease in serum cholesterol concentration after acute myocardial infarction.[8] In the study by Mendez et al,[2] diabetic subjects had been excluded. Our different findings may be a result of our including diabetic patients. However, excluding the 29 diabetic patients from our analysis did not alter the result.

We included more patients than previous studies. Moreover, we examined concentrations of apolipoprotein subfractions and lipoprotein (a), and we compared changes in the lipid profiles of patients with different stroke subtypes. Since the lipid profile did not vary with age or sex in our patients, the results from all patients were grouped together. Acute intracerebral hemorrhage appeared to have little effect on the serum lipid profile, whereas cerebral infarction was associated with initial elevation of the cholesterol, LDL-C, and Apo B concentrations and depression of the triglyceride and lipoprotein (a) concentrations. Changes in Apo B concentration should parallel those of LDL-C, and changes in Apo A_1 concentration should parallel those of HDL-C. Although this was observed for patients with cerebral infarction, Apo B concentration did not appear to follow the changes in LDL-C concentration for patients with lacunar infarction. Nevertheless, their mean Apo B concentration was lower 3 months later, although not significantly so, probably due to the large standard deviations and small sample size. A large standard deviation may also account for similar discrepancies in the HDL_3-C and Apo A_1 concentrations for patients with intracerebral hemorrhage and for all strokes.

It could be argued that as a consequence of stroke, there may be a change in dietary habit, resulting in "improvement" of the lipid profile over the subsequent 3 months. We did not assess our patients' dietary habits before and after stroke. Nevertheless, it has been shown that in Hong King, the percentage of calorie intake as fat for elderly Chinese varies from 15% to 20%, which is much lower than that among Caucasians (approximately 40%),[9] so changes in fat intake is unlikely to modify the lipid profile. Ideally, one should be able to measure the lipid profile immediately before, immediately after, and then perhaps 3 months after acute stroke to assess clearly the effect of acute stroke. However, this would not be practicable.

The mechanism of lipid changes remains unclear, but it is thought to relate in part to the stress and associated catecholamine overproduction of acute stroke.[10] However, serum cholesterol concentration is usually lowered with increasing catecholamine levels,[2] and as such would not explain our observations. Moreover, if stress or severity of stroke

accounted for our findings, we would expect patients with a lower Glasgow Coma Scale score and those who died to have higher serum cholesterol, LDL-C, and Apo B concentrations. However, the opposite was found; all these values were lower in patients with a Glasgow Coma Scale score of <10 and in those who died.

Due to the temporal changes in lipid profile after acute stroke, studies examining lipids as risk factors for stroke using blood samples collected ≤48 hours after ictus may incorrectly identify lipid fractions as risk factors. It would be more appropriate to use 3-month follow-up values for comparison with control subjects.

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KEY WORDS • lacunar infarction • cerebral hemorrhage • cholesterol