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Serum cholesterol levels and survival after rtPA treatment in acute stroke

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Background: According to the reverse epidemiology hypothesis, high cholesterol levels might be protective and associated with greater survival rates under certain conditions. In stroke patients, a clear correlation between lipid levels and mortality after ischaemic and hemorrhagic strokes has been demonstrated. The aim of this study was to analyze the impact of lipid levels on 3-month mortality in patients with ischaemic stroke (IS) homogeneously treated with intravenous rtPA and admitted to a monitored acute stroke unit.

Methods: Retrospective analysis of a prospective cohort of 220 patients with an IS treated with rtPA within the first 4.5 h in a single tertiary hospital from January 2005 to August 2010.

Results: Mortality at 3 months was 15.0%. Univariate analysis showed that age, NIHSS at admission, heart failure, and atrial fibrillation were directly related to 3-month mortality; cholesterol, triglycerides, and low density lipoprotein were inversely associated. The death rate by cholesterol level was 5.5% for the highest tertile (>192 mg/dl), 13.7% for the middle (192–155 mg/dl), and 25.7% for the lowest (<155 mg/dl), $P = 0.003$. Multivariate analysis showed that amongst the lipid determinations, only cholesterol [OR: 0.985 (95% CI: 0.972–0.998), $P = 0.021$] was inversely associated with 3-month mortality. The 'protective' effect of cholesterol was independent of stroke severity and remained significant in non-lacunar strokes.

Conclusions: Survival of stroke patients receiving current, most effective medical treatment is related to blood cholesterol levels, with an inverse relationship between cholesterol and mortality. The mechanism of this apparently paradoxical situation remains unexplained but merits further research.

Introduction

The relationship between lipids and stroke has been analyzed from many different perspectives and is full of paradoxes and controversial results. First, whereas epidemiological data have clearly demonstrated the role of cholesterol in coronary artery disease, development, and mortality [1,2], the relationship with ischaemic stroke (IS) is less clear owing to inconsistent data [2,3]. Secondly, low cholesterol levels are related to other stroke subtypes such as subarachnoid hemorrhage [4] and intracerebral hemorrhage [5]. Thirdly, a paradoxical relationship between lipid levels and stroke outcome has been observed in IS [6], in men (but not women) with acute IS [7] and in cerebral hemorrhage [8], providing an example of 'reverse epidemiology,' a term used to describe the fact that some cardiovascular risk factors, such as obesity, hypercholesterolemia, and hypertension, are not harmful but rather permit better survival in the elderly or in some chronic diseases [9]. This phenomenon is poorly understood but has been observed in patients with cancer, chronic heart failure (HF), and end-stage renal disease. Fourthly, the impact of statin pretreatment is linked with a better outcome in IS [10] and in hemorrhagic stroke [11]. Fifthly, the effect of pretreatment with statins [12–14] or history of dyslipidemia [15] has been analyzed in relation to the results of systemic rtPA [12,13] and endovascular treatment [14,15], with conflicting results. Finally, hyperlipidemia is an independent factor related to reduction in white matter hyperintensity volume in patients with IS [16].

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Concerning the role of cholesterol in IS outcome, the large studies that have analyzed this relationship [6,7,10] included patients who differed in time of evolution at admission and were not homogeneously treated. The aim of our study is to analyze whether a relationship between acute lipid values and 3-month mortality is observed in a prospective cohort of acute stroke patients, all homogeneously treated with intravenous rtPA and admitted to a stroke care monitoring unit.

Methods

From January 2005 to August 2010, 236 patients with acute IS were treated with intravenous rtPA within the first 4.5 h of admission to a single tertiary hospital. All patients were prospectively included in the BasicMar database [17], an ongoing register of patients with acute stroke at our hospital. We excluded 16 cases because of incomplete data: no lipid determinations (11 cases) and lost to follow-up (5 cases). The final study cohort included 220 cases (93.2% of the series).

All patients received a computed tomography (CT) scan in the emergency room. Initial stroke severity was assessed at hospital admission by a trained neurologist using the National Institutes of Health Stroke Scale (NIHSS). The lipid profile was routinely obtained from fasting patients on the morning after admission. All analyses were performed in our local laboratory. Stroke subtype was categorized using the TOAST classification, following a neurovascular study that included carotid and transcranial ultrasound, angio-magnetic resonance imaging (MRI), and 24-h electrocardiogram (EKG) monitoring. Additional CT or MRI evaluations were made, if needed, during hospitalization. Transthoracic or transesophageal echocardiography was performed in patients with strokes of undetermined origin. All patients were admitted to our monitored stroke unit, a four-bed semi-intensive care unit in which bedside monitors continuously record vital functions. Neurological status was assessed every 6 h for the first 24 h and once a day thereafter. The outcome was assessed at 3 months, either by hospital visit or through telephone interview, using the modified Rankin scale (mRS). All patients but one had a CT scan at 24 h after rtPA treatment to evaluate the presence of ischaemic lesions or hemorrhagic complications. We used the ECASS criteria [18] to define the hemorrhagic transformation: HI petechial infarction without space-occupying effect; HI1, small petechiae; HI2, more confluent petechiae; PH, hemorrhage (coagulum) with mass effect; PH1, $<30\%$ of the infarcted area with mild space-occupying effect; and PH2, $>30\%$ of the infarcted area with significant space-occupying effect. If the hemorrhage was remote, it was classified as rPH.

Factors analyzed

Vascular risk factors were obtained from the patient, relatives, caregivers, or previous medical records, following the definitions recommended by the international guidelines. Risk factors were registered in a structured questionnaire as follows: arterial hypertension (evidence of at least two raised blood pressure measurements, systolic >140 mmHg or diastolic >90 mmHg, recorded on different days before stroke onset; a physician's diagnosis; or use of medication); diabetes (physician diagnosis or use of medication); hyperlipidemia [physician diagnosis, use of medication, serum cholesterol concentration >220 mg/dl, low density lipoprotein cholesterol (LDL-c) >130 mg/dl or serum triglyceride concentration >150 mg/dl]; current smoking habits; ischaemic heart disease (documented history of angina pectoris or myocardial infarction); HF; and atrial fibrillation (AF) (physician diagnosis, use of medication; or conclusive echocardiogram data). We also recorded previous treatment with statins or antiplatelet drugs.

We analyzed the relationship between death at 3 months and age, sex, initial stroke severity, vascular risk factors, previous treatment, glycemia at admission ($n = 220$), and lipid determinations at 12–48 h after stroke [cholesterol, $n = 220$; triglycerides, $n = 220$; LDL-c, $n = 191$; and high density lipoprotein cholesterol (HDL-c), $n = 188$]. The relationship between lipid levels, and stroke subtype, stroke severity and hemorrhagic transformation was also evaluated. Finally, to avoid any bias owing to the relationship between lacunar strokes, cholesterol levels, and mortality, we repeated the analysis after excluding lacunar stroke cases.

Statistical analysis

Total cholesterol and LDL-c presented a normal distribution and were expressed as the mean $\pm$ standard deviation. Age, NIHSS, glycemia, triglycerides, and HDL-c presented a non-normal distribution and were expressed as the median (quartile 1, quartile 3). Categorical data were expressed as real numbers and percentages. Differences in parametric and nonparametric continuous variables were evaluated using the t test and the Mann–Whitney U test, respectively, and the chi-square test was used for proportional analysis.

To analyze the relationship between lipid levels and stroke subtype, we used the Kruskal–Wallis test (only patients with atherothrombotic, lacunar, or cardioembolic strokes were included).

To analyze the relationship between lipid levels and stroke severity, we performed the Spearman correlation test.

Multivariable ORs with 95% CI were calculated by an independent stepwise logistic regression model for each lipid. In a second step, we repeated the analysis after excluding the lacunar stroke cases ($n = 22$). The analysis was adjusted for all variables that showed an association with 3-month mortality with a $P < 0.1$ in the univariate analysis. TOAST stroke subtype was not included given the absence of linear correlation between TOAST and any impact on mortality, because there was an interaction between TOAST subtypes and stroke severity.

The variables were cross-tabulated to assess multicollinearity. All analyses were two-tailed. The significance level was set at 0.05.

Ethics

The information used in this study was collected from the prospective register BasicMar, with the approval of our local ethics committee. All patients gave their informed consent prior to their inclusion in the study.

Results

The study included 220 patients, 115 men and 105 women. Table 1 shows the baseline data. Mortality was higher in cardioembolic stroke (29.1%) than in atherothrombotic stroke (17.1%), unusual causes of stroke (8.3%), cryptogenic stroke (2.9%), or lacunar stroke (0%). Cause of death was neurological in 12 cases (cerebral edema/neurological deterioration in 11 cases and hemorrhagic transformation in 1 case), non-neurological in 19 cases (respiratory causes in 11 cases, cardiac/sudden death in 5 cases, 1 multiorganic failure, 1 renal failure, and 1 pulmonary thromboembolism) and of unknown cause in 2 cases. Cardioembolic patients more frequently died owing to non-neurological (63%) than atherothrombotic (40%) causes, but the difference was not significant ($P = 0.620$).

Table 1 Demographics and baseline data of the series

Age, years, median (q1, q3)	73 (64, 80)
Sex (m), *n* (%)	115 (52.3)
Arterial hypertension, *n* (%)	137 (62.3)
Diabetes mellitus, *n* (%)	61 (27.7)
Hyperlipidemia, *n* (%)	97 (44.1)
Previous coronary artery disease, *n* (%)	44 (20.0)
Previous stroke/TIA, *n* (%)	31 (14.1)
Heart failure, *n* (%)	20 (9.1)
Atrial fibrillation, *n* (%)	73 (33.2)
Current smoking, *n* (%)	55 (25.0)
Alcohol overuse, *n* (%)	27 (12.3)
Previous antiplatelet treatment, *n* (%)	87 (39.5)
Previous statin treatment, *n* (%)	67 (30.5)
Glycemia at admission, mg/dl, median (q1, q3)	117 (101, 153)
Cholesterol, mg/dl, mean (SD)	174.8 (42.9)
Triglycerides, mg/dl, median (q1, q3)	105 (79, 137)
LDL-c, mean mg/dl (SD)	104.3 (36.5)
HDL-c, mg/dl, median (q1, q3)	49 (40, 56)
Atherothrombotic stroke, *n* (%)	35 (15.9)
Lacunar stroke, *n* (%)	22 (10.0)
Cardioembolic stroke, *n* (%)	79 (35.9)
Unusual stroke, *n* (%)	12 (5.5)
Undetermined stroke, *n* (%)	72 (32.7)
NIHSS at admission, median (q1, q3)	12 (8, 19)
Hemorrhagic transformation, *n* (%)	38 (17.4)
Death at 3 months, *n* (%)	33 (15.0)

Univariate analysis of factors associated with 3-month mortality is shown in Table 2. The death rate by cholesterol level was 5.5% for patients in the highest tertile (>192 mg/dl), 13.7% in the middle (192–155 mg/dl), and 25.7% in the lowest (<155 mg/dl), $P = 0.003$ (Fig. 1).

Lipid levels and glycemia at admission differed by TOAST stroke subtype (Table 3).

Stroke severity has an inverse relationship with cholesterol ($P = 0.004$, $r = -0.195$); triglycerides ($P < 0.0001$, $r = -0.247$); and LDL-c ($P = 0.001$, $r = -0.229$). There was no relationship with HDL-c ($P = 0.225$, $r = 0.089$).

Logistic regression models for 3-month mortality were performed separately for cholesterol, triglycerides, LDL-c, and hyperlipidemia and adjusted for age, NIHSS, current smoking, AF, and HF. Dyslipidemia was not included owing to collinearity with lipid determinations. Results are detailed in Table 4, showing that amongst lipid determinations, only cholesterol was inversely related to outcome: [OR: 0.985 (95% CI: 0.972–0.998), $P = 0.021$].

Excluding the lacunar stroke cases ($n = 22$) did not significantly affect results for the following factors associated with 3-month mortality: cholesterol [OR: 0.985 (95% CI: 0.972–0.998), $P = 0.025$]; age [OR 1.055 (95% CI: 0.997–1.116), $P = 0.062$]; NIHSS [OR 1.259 (95% CI: 1.129–1.404), $P < 0.0001$].

Hemorrhagic transformation was seen in 38 cases (17.4%), including 23 HI1 cases, 4 HI2, 5 PH1, and 6 rPH. There were no significant associations between hemorrhagic transformation and any lipid value, glycemia, previous antiplatelet or statin treatment, vascular risk factors or age. The only related factor was NIHSS at admission: 12 (7, 18) vs. 18 (11, 20), respectively, $P = 0.014$.

Discussion

The results of this study show that higher cholesterol levels are associated with better chances for survival and lesser stroke severity in a cohort of stroke patients treated with systemic rtpA plus admission to a stroke

Table 2 Univariate analysis of factors related to 3-month death

	Alive (n = 187)	Dead (n = 33)	P	OR	95% CI
Age, years, median (q1, q3)	72 (62, 79)	80 (74, 86)	0.0001		
Sex (m), n (%)	99 (86.1)	16 (13.9)			
Sex (f), n (%)	88 (83.8)	17 (16.2)	0.707		
Arterial hypertension, n (%)	114 (61.0)	23 (69.7)	0.437		
Diabetes mellitus, n (%)	52 (27.8)	9 (27.3)	0.999		
Hyperlipidemia, n (%)	89 (47.6)	8 (24.2)	0.014	0.35	0.15–0.82
Previous coronary artery disease, n (%)	36 (19.3)	8 (24.2)	0.487		
Previous stroke/TIA, n (%)	24 (12.8)	7 (21.2)	0.274		
Heart failure	13 (7.0)	7 (21.2)	0.017	3.60	1.32–9.87
Atrial fibrillation, n (%)	51 (27.3)	22 (66.7)	0.0001	5.33	2.42–11.78
Current smoking, n (%)	51 (27.3)	4 (12.1)	0.081	2.25	0.87–5.81
Alcohol overuse, n (%)	25 (13.4)	2 (6.1)	0.387		
Previous antiplatelet treatment, n (%)	69 (36.9)	18 (54.1)	0.108		
Previous statin treatment, n (%)	59 (31.6)	8 (24.2)	0.539		
Glycemia at admission, mg/dl, median (q1, q3)	115 (100, 149)	124 (108, 167)	0.095		
Cholesterol, mean mg/dl (SD)	179.3 (42.5)	149.7 (36.0)	0.0001		
Triglycerides, mg/dl, median (q1, q3)	107 (83, 145)	85 (63–107)	0.005		
LDL-c, mean mg/dl (SD)	107.8 (36.5)	81.3 (27.1)	0.001		
HDL-c, mg/dl, median (q1, q3)	49 (40, 56)	49 (41, 62)	0.575		
NIHSS at admission, median (q1, q3)	11 (7, 16)	20 (18, 22)	0.0001		
Hemorrhagic transformation, n (%)	30 (16.0)	8 (25.0)	0.214		

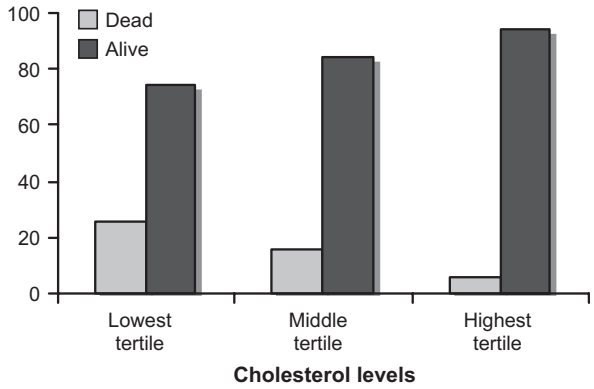

Figure 1 The 3-month mortality decreases according to cholesterol tertile, from 25.7% in the lowest (< 155 mg/dl) to 13.7% in the middle (155–192 mg/dl) and 5.5% in the highest (> 192 mg/dl), P = 0.003.

care monitoring unit. Factors related to mortality and poor outcome after IS included age [19], stroke severity [20], history of AF [21] or HF [22], atherosclerotic burden [23], hyperglycemia [24], low cholesterol levels [25], and low triglyceride levels [26]. The determinants are very similar in patients treated with rtPA, but other factors such as the site of the occlusion [27], successful recanalization [28], and time to treatment [29] also play an important role.

Our results agree with previous data [30]: stroke severity is the main determinant of 3-month mortality in patients treated with rtPa; age and AF appear in some of the models, and there is a trend for HF (Table 4). Interestingly, despite acute aggressive treatment (systemic rtPA and monitored acute care in a stroke unit), cholesterol level has an inverse relationship with mortality similar to unselected IS patient series [7,8,25]. A better outcome has been described [12] in patients pretreated with statins, but in agreement with another report [13], we found no such relationship in our cohort of rtPA-treated patients. In fact, we observed no relationship between any lipid determination and any effect of statin pretreatment on hemorrhagic transformation.

Although the particular inverse relationship between 'bad lipids' and better outcome after stroke is intriguing and difficult to explain, the same finding has been reported for IS [7,8,25], intracerebral hemorrhages [9], and leukoaraiosis [16]. A similar relationship has been

Table 3 Lipid and glucose values according to the TOAST stroke subtypes

	Lacunar	Atherothrombotic	Cardioembolic	P
Cholesterol, mean (SD)	202.6 (46.7)	181.2 (37.8)	161.3 (39.6)	0.0001
Triglycerides, median (q1, q4)	145 (107, 175)	132.5 (84, 168)	86 (66, 115)	0.0001
LDL-c, mean (SD)	131.0 (35.7)	110.4 (34.4)	90.4 (35.8)	0.0001
HDL-c, median (q1, q4)	45.5 (36, 54)	49.5 (39, 55)	49 (41, 53)	0.375
Glucose, median (q1, q4)	106 (98, 157)	145 (111, 209)	117 (100, 160)	0.038

Table 4 Multivariate regression analysis of factors related to 3-month mortality

	P	OR	95% CI
Model 1			
Cholesterol	0.021	0.985	0.972–0.998
Age	0.066	1.054	0.997–1.115
NIHSS	0.0001	1.267	1.136–1.413
Current smoking	0.476	0.599	0.146–2.452
Heart failure	0.166	2.393	0.696–8.225
Atrial fibrillation	0.114	2.148	0.833–5.540
Model 2			
Triglycerides	0.330	0.994	0.981–1.007
Age	0.038	1.059	1.003–1.119
NIHSS	0.0001	1.267	1.137–1.413
Current smoking	0.774	0.812	0.197–3.349
Heart failure	0.062	3.310	0.994–10.246
Atrial fibrillation	0.126	2.053	0.818–5.157
Model 3			
LDL-c	0.234	0.988	0.968–1.008
Age	0.114	1.055	0.987–1.129
NIHSS	0.0001	1.377	1.166–1.627
Current smoking	0.799	0.795	0.137–4.617
Heart failure	0.300	2.357	0.466–11.917
Atrial fibrillation	0.013	4.450	1.371–14.449
Model 4			
Hyperlipidemia	0.172	0.496	0.181–1.356
Age	0.035	1.060	1.004–1.119
NIHSS	0.0001	1.271	1.142–1.415
Current smoking	0.770	0.815	0.207–3.207
Heart failure	0.077	2.985	0.889–10.026
Atrial fibrillation	0.133	2.030	0.806–5.117

described in other neurological diseases such as Alzheimer's and Parkinson's [31].

Our study does not allow us to identify the reason why low cholesterol is associated with increased mortality after IS, although we could hypothesize that this is an epiphenomenon or a surrogate marker of poor prognosis rather than an effect related to cholesterol levels. However, cholesterol is one of the most important regulators of lipid organization, is essential for normal membrane functionality, and is also an important component of the so-called lipid rafts or microdomains with a pivotal role in cell membrane function. To explain cholesterol's apparent 'good effect' on the brain, it has been argued that cholesterol has neuroprotective properties, may act as a buffer neutralizing free radicals and providing antioxidant protection [32], is able to modulate the endothelial repair process [33], and plays a crucial role in the development of the central nervous system and in the creation and maintenance of new synapses [34]. High cholesterol would result in better neuron survival in cerebral areas such as the forebrain cholinergic system, hippocampus, and some neocortical areas [35]. Many important membrane-signaling proteins are located within the raft regions of the membrane, and alterations in lipid raft structure can alter the activity of these signaling proteins [36]. In patients with acute stroke, it seems plausible that plasmatic cholesterol would play a 'neuroprotective' effect. The breakdown of the brain–blood barrier might permit cholesterol, as well as other lipids, to reach the central nervous system. The capacity to synthesize cholesterol would be difficult to maintain if the brain were damaged, and precisely when the need for cholesterol synthesis would be much higher than in the uninjured state [37]. Alternatively, older neurons may lose their capacity to synthesize cholesterol [38], increasing the intracerebral lost of cholesterol. Finally, brain endothelial cells have the potential to take up LDL-c through luminal LDL receptors and translocate this LDL across the cell [39]; therefore, it is possible that the effect of cholesterol would be mediated at the cerebral microcirculation level rather than at the level of glial cells or neurons [37].

Another interesting but unexplained finding is the inverse relationship between cholesterol and stroke severity [40], a finding that is supported by our results showing that not only cholesterol but also triglyceride and LDL-c levels are inversely related to stroke severity. It has been suggested that higher cholesterol favors the development of small-vessel disease and thereby less severe strokes associated with lower mortality [40]. Despite clear differences between TOAST subtypes in lipid levels (Table 3), this did not explain the 'protective' association of lipids and stroke survival in our results because the relationship between cholesterol and mortality was independent of stroke severity and, moreover, remains unchanged after excluding the lacunar stroke cases.

This study has some limitations attributable to the retrospective design, relatively small number of cases, and impossibility of adjusting the results by TOAST subtype (there is no linear correlation). On the other hand, the study has strengths that should be acknowledged. All patients were admitted to a monitored stroke unit and treated with systemic rtPA. The lost cases rate is very low (6.8%), our analysis was adjusted for the most important determinants of mortality (stroke severity and age), and a subanalysis excluded lacunar strokes.

Conclusions

The main result of this study is the inverse relationship between cholesterol and 3-month mortality in stroke patients, showing that survival is associated with high blood cholesterol levels, despite treatment with the current most effective medical treatment. The mechanism of this apparent paradox, common to both

ischaemic and hemorrhagic strokes, remains unexplained, and merits further research.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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