

Higher Serum Total Cholesterol Levels are Associated With Better Long-Term Balance Function After First-Time Ischemic Stroke

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Abstract

Background: To investigate the effects of serum total cholesterol (TC) on long-term balance function in patients with first-time ischemic stroke.

Methods: A total of 99 patients with first-time ischemic stroke were enrolled. The participants were divided into two groups according to TC levels: high TC (≥ 5.17 mmol/L) and low TC (< 5.17 mmol/L). Balance function was measured using the Postural Assessment Scale for Stroke Patients (PASS) at 2 weeks (baseline) and 1, 3, 6, and 12 months after stroke. Prognostic factors affecting the repeated measurements of the PASS score were evaluated using linear mixed regression analysis.

Results: TC levels, baseline PASS score, age, sex, and follow-up time were identified as significant prognostic factors of the long-term PASS score. The high TC group had higher PASS scores (estimated parameter 1.57, 95% CI: 0.58, 2.55) than the low TC group. An increase of one unit in the baseline PASS score led to a 0.65 unit increase (95% CI: 0.61, 0.70) in subsequent PASS scores. Age was negatively correlated with the PASS scores, with a 0.12 unit decrease (95% CI: -0.16, -0.07) for a 1 year increase in age. Women had PASS scores that were 2.63 units lower (95% CI: -3.70, -1.57)

than men.

Conclusions: Higher serum TC levels measured during the acute stage of first-time ischemic stroke are a favorable prognostic factor for long-term balance function.

Keywords: Cholesterol; Stroke; Rehabilitation; Postural balance; Risk factors

Introduction

Stroke-related neurological deficits and disability are an enormous burden to healthcare systems, underscoring the importance of predicting outcomes during the early stage of stroke [1]. While high serum total cholesterol (TC) levels have been shown to increase the risk of coronary artery disease [2], the association between hypercholesterolemia and stroke remains controversial [3-8]. Moreover, several previous studies have pointed out the paradoxical finding that higher serum TC levels are related to lower mortality after stroke [9-12]. Zuliani et al [11] reported that stroke patients with low serum TC levels have higher short-term mortality and Olsen et al [12] showed that higher TC levels are associated with less severe stroke and a higher ten-year survival. In contrast, several groups failed to demonstrate such a favorable prognostic effect of high TC levels in stroke patients [13-15]. These conflicting findings may be partly explained by heterogeneity within and across study populations [9, 14]. Since cholesterol might play different roles in ischemic stroke and hemorrhagic stroke [16], it is necessary to evaluate outcome in a more homogeneous population (e.g. individuals with first-time ischemic stroke). In addition, most previous studies on the prognostic role of TC on stroke evaluated mortality [9-12, 14, 15] or short-term disability [10, 17] as the outcome measure. Little is known about the relationship between serum TC levels and long-term functional performance in stroke survivors. To the best of our knowledge, no study has specifically evaluated the prognostic value of serum TC levels on balance function in a stroke population. The Postural Assessment Scale for Stroke

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Table 1. Demographic and Clinical Characteristics of the Participants Stratified by Total Cholesterol Level

Variables	HTC group (n = 54)	LTC group (n = 45)	P value
Age, y	68.3 ± 9.7	65.0 ± 11.8	0.130
Women	23 (42)	13 (29)	0.158
Baseline PASS score	20.1 ± 11.5	19.0 ± 11.0	0.788
Diabetes mellitus	20 (37)	13 (29)	0.392
Coronary artery disease	11 (20)	6 (13.3)	0.355
Left side lesion	32 (59)	27 (60)	0.940
Basal ganglion lesion	24 (44)	15 (33)	0.353
Large infarct	43 (80)	37 (82)	0.297
Glucose, mmol/L	7.69 ± 2.86	6.92 ± 3.17	0.260
Albumin, g/L	37 ± 3	36 ± 5	0.516
Creatinine, μmol/L	78.68 ± 21.22	84.87 ± 26.52	0.234

The values are expressed as the number (%) or the mean ± standard deviation. Abbreviations: PASS: Postural Assessment Scale for Stroke Patients; HTC, high total cholesterol (≥ 5.17 mmol/L); LTC, low total cholesterol (< 5.17 mmol/L).

patient (PASS), a clinical assessment of postural control in stroke patients, has been proven to be a valid indicator of functional recovery in stroke patients [18-21]. In this study, we investigated the effect of serum TC levels on long-term PASS scores in patients with first-time ischemic stroke. Such information should be very informative in clinical consultation and rehabilitation planning.

Methods

The data were taken from the registry of the “Quality of Life after Stroke Study” (QLSS) for the period between November, 1999 and November, 2001. The QLSS is a prospective

cohort study of stroke patients admitted to the National Taiwan University Hospital (NTUH) and the details of the QLSS have been described elsewhere [18]. The study was approved by the National Taiwan University Hospital (NTUH) Research Ethics Committee. Written informed consent was obtained from each participant. Patients were included if they met the following criteria: (1) first-time diagnosis of ischemic stroke defined according to the International Classification of Disease, 9th Revision, clinical Modification codes of cerebral infarction (434) or others (433, 436, 437); (2) arrival at the hospital within 14 days after stroke onset; (3) able to obey commands; and (4) signed informed consent. A total of 99 patients with first-time ischemic stroke were enrolled.

As the outcome measure, we used the PASS, which con-

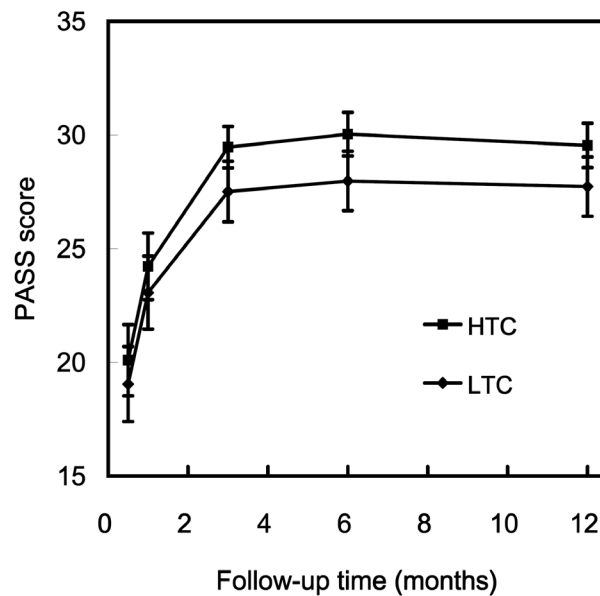


Figure 1. PASS scores during follow-up after stroke. The data are presented as the mean \pm SEM. Abbreviations: HTC, high total cholesterol (≥ 5.17 mmol/L); LTC, low total cholesterol (< 5.17 mmol/L); PASS, Postural Assessment Scale for Stroke Patients.

sists of 12 four-level items that are used to grade performance in maintaining or changing a given posture in situations of varying difficulty [19, 21]. The total PASS score ranges from 0 to 36, with a higher score indicating a better balance function [19]. Each patient underwent repeated PASS measurements at 2 weeks (baseline), 1 month, 2 months, 6 months, and 1 year after stroke. One occupational therapist, who was blinded to the laboratory data, administered the PASS to all patients. All subjects underwent a regular rehabilitation training program during hospitalization, including physical therapy, occupational therapy, and nurse support. The size of the infarct was determined by the largest diameter of the lesion on neuroimages, such as computerized tomography and magnetic resonance imaging. Laboratory examinations, including serum TC and other biochemical tests, were performed in the same laboratory of the NTUH within two weeks after stroke onset. Serum levels of TC and albumin were measured using an automatic biochemical analyzer (Hitachi 7450; Hitachi, Tokyo, Japan). The concentration of plasma glucose was measured using an autoanalyzer (Hitachi 7170; Hitachi Corp., Tokyo, Japan).

We evaluated the association between serum TC levels and long-term balance function after ischemic stroke. Other factors that were evaluated in the analysis included demographic factors (age and sex), medical comorbidities (diabetes mellitus and coronary artery disease), biochemical variables (glucose and albumin levels), infarct location, infarct size, and laterality of brain lesions. Because basal ganglia lesions may be associated with an unfavorable functional outcome [22], we grouped the location of the infarct according

to involvement of the basal ganglion. Lesions greater than 1 cm in size were defined as large infarcts.

Statistical method

The participants were grouped into the high TC (HTC, total cholesterol ≥ 5.17 mmol/L) and low TC (LTC, total cholesterol < 5.17 mmol/L) groups. Demographic and clinical characteristics were compared between the groups using Student's t test for interval variables and the chi-square test for categorical variables. The linear mixed regression model was used to analyze the effects of various prognostic factors on the repeated measurements of the PASS. Because the rate of functional recovery following stroke tended to be initially faster, then decrease with time, a natural logarithm transformation was applied to the follow-up time as $\log(\text{days})$ for approximating a linear relationship between the PASS score and follow-up time. The statistical criterion for eliminating the variable from the stepwise analysis was a significance level > 0.10 . An alpha level of 0.05 was considered statistically significant for all analyses. The analysis was carried out using SAS software (release 9.1, SAS Institute Inc, Cary, NC).

Results

Table 1 shows the demographic and clinical characteristics of the subjects, stratified by TC levels. The mean TC levels were 6.04 mmol/L for the HTC group and 4.41 mmol/L

Table 2. Analysis of Prognostic Factors Affecting Repeated Measurements of the PASS Score Using a Linear Mixed Regression Model

Variable [†]	Regression coefficients			
	Crude [‡] (95% CI)	P value	Multiple regression (95% CI)	P value
Follow-up time in log(days)	2.94 (2.24, 3.65)	< 0.0001	2.94 (2.53, 3.35)	< 0.0001
Age (year)	-0.15 (-0.23, -0.08)	< 0.0001	-0.12 (-0.16, -0.07)	< 0.0001
Sex (female vs. male)	-1.92 (-3.65, 0.18)	0.031	-2.63 (-3.70, -1.57)	< 0.0001
Baseline PASS score	0.66 (0.61, 0.70)	< 0.0001	0.65 (0.61, 0.70)	< 0.0001
Total cholesterol (HTC vs. LTC)	2.01 (0.32, 3.69)	0.020	1.57 (0.58, 2.55)	0.002
Lesion laterality (left vs. right)	0.18 (-1.52, 1.88)	0.831	ND	ND
Basal ganglion lesion (yes vs. no)	-1.40 (-3.14, 0.35)	0.118	ND	ND
Lesion size (\geq 1 cm vs. < 1 cm)	-6.33 (-8.74, -3.92)	< 0.0001	ND	ND
Diabetes mellitus (yes vs. no)	-0.88 (-2.63, 0.87)	0.325	ND	ND
Coronary artery disease (yes vs. no)	-2.39 (-4.57, -0.21)	0.032	ND	ND
Albumin (< 35 vs. \geq 35 g/L)	-0.96 (-3.12, 1.20)	0.386	ND	ND
Glucose (\geq 11.1 vs. < 11.1 mmol/L)	-2.76 (-5.48, -0.05)	0.047	ND	ND

[‡]Only adjusted for follow-up time. [†]The value or group on the right-hand side of each comparison is the reference group. Abbreviations: PASS, Postural Assessment Scale for Stroke Patients; HTC, high total cholesterol (\geq 5.17 mmol/L); LTC, low total cholesterol (< 5.17 mmol/L); ND, no data.

for the LTC group. The follow-up rates for the HTC and LTC groups at the end of the study were 91% and 92%, respectively. There was no significant difference between the

HTC and LTC groups in demographic variables (age, sex) or clinical variables (baseline PASS score, diabetes mellitus, coronary artery disease, infarct laterality, infarct size, basal

ganglion infarct, glucose, and albumin).

Figure 1 shows the changes in the PASS score with time for the LTC and HTC groups. For both groups, the PASS score increased rapidly in the first three months, then reached a plateau. The HTC group had a higher mean PASS score than the LTC group at all time points, showing that subjects with higher TC levels have better postural control after stroke.

The results of linear mixed regression analysis for the repeated measurements of the PASS score are presented in Table 2. The estimate of the crude effect (only adjusted for the follow-up time) of each variable analyzed is shown on the left and the adjusted parameter estimates of the final multiple regression model on the right. TC levels ($P = 0.0020$), follow-up time ($P < 0.0001$), age ($P < 0.0001$), sex ($P < 0.0001$), and baseline PASS score ($P < 0.0001$) were significant prognostic factors for the serial PASS scores in the final multiple regression model. Other independent variables, including lesion laterality, infarct location, infarct size, diabetes mellitus, coronary heart disease, glucose, and albumin had no significant effect on the PASS score in the multiple regression analysis. For the continuous variables (age, baseline PASS score, and follow-up time), the estimated parameters indicate the magnitude of the change in subsequent PASS scores for each 1 unit change in the corresponding variable. For the categorical variables (sex and cholesterol), the estimated parameters represent the differences in PASS scores compared to the reference group (Table 2).

TC levels had a significant positive effect on the serial measurements of the PASS score. The HTC group had better balance function (estimated parameter 1.57, 95% CI: 0.58, 2.55) than the LTC group. PASS scores increased with follow-up time, with an increase of one unit of log-transformed day correlating with an increase of 2.94 units (95% CI: 2.53, 3.35) in the PASS score. An increase of one unit in the baseline PASS score correlated with an increase of 0.65 units in subsequent PASS scores (95% CI: 0.61, 0.70). Age and sex were significant predictors of PASS: older subjects had lower PASS scores with an estimate of a decrease of 0.12 units in the PASS scores (95% CI: -0.16, -0.07) for a 1 year increase in age, while women had PASS scores 2.63 units lower than men (95% CI: -3.70, -1.57).

Discussion

The main finding of our study was that high serum TC levels measured during the acute stage of stroke were significantly correlated with better long-term balance function in patients with first-time ischemic stroke. The favorable effects of TC remained significant after controlling for other prognostic factors. There are no established biologically plausible mechanisms to explain the finding that higher serum TC levels correlate with higher long-term PASS scores in patients

with first-time ischemic stroke. However, we propose several explanations below.

Firstly, cholesterol has been reported to have a neuroprotective effect because of its anti-oxidative properties [23, 24]. Bastiaanse et al [25] found that high cholesterol levels enhance the adaptation of cardiac myocytes to ischemia in vitro, while Joseph et al [24] demonstrated that high cholesterol levels reduce oxidative stress for brain tissue in vitro. When brain tissues undergo ischemic insult, the neural cells produce free radicals, which destroy the lipid bilayer of cell membranes, and cholesterol may serve as a buffer to neutralize the free radicals and protect brain tissues from ischemic injury.

Another possible explanation is that higher serum TC levels could be associated with minor ischemic stroke, which may result in better long-term postural control. Amarenco et al [26] found that lacunar stroke is associated with higher serum cholesterol and, more recently, Olsen et al [12] reported that higher TC levels are associated with less severe stroke. However, this hypothesis may not explain the favorable prognostic effect of high TC levels seen in our study, because the proportion of large infarcts and the baseline PASS scores, both of which indicate initial stroke severity, did not differ significantly between the HTC and LTC groups. Moreover, the effects of TC levels remained significant after controlling for the influences of infarct size and baseline PASS scores.

Finally, low serum TC levels may reflect poor nutrition and health status, which could account for the unfavorable outcomes associated with low TC levels. Kronmal et al [27] and Weverling-Rijnsburger et al [28] found that the all-cause mortality was higher in old patients with low cholesterol and suggested that low TC levels could be accompanied by frailty. However, in the present study, there was no significant difference in serum albumin levels or medical comorbidities between the HTC and LTC groups. These findings do not support the idea that the association between low TC and poor postural control was due to poor general health status or malnutrition.

In addition to TC levels, we found that baseline PASS score, age, and sex were significant prognostic factors for long-term balance function. The baseline PASS score, which represents the initial balance function after stroke, significantly affected subsequent PASS scores. It should be noted that TC levels remained a significant independent predictor after adjusting for the baseline PASS score. Older age has been reported to correlate with poor long-term functional outcome after stroke [29-35] and our study also showed that older participants had poorer balance function. One possible explanation is that older patients may have higher risk of complications and a lower potential for neural reorganization after stroke, which could lead to unfavorable functional outcomes [33].

We also found that women had significantly poorer balance function than men. The prognostic role of sex on

functional outcomes after stroke has been debated in the literature [36-40]. Further studies are required to clarify this association.

Study Limitations

Detailed information on statin use before and after stroke was lacking in our study. Nevertheless, in most clinical practice, only patients with high TC levels would take statins for the secondary prevention of ischemic stroke. However, such therapeutic intervention for hypercholesterolemia would be expected to weaken the association between high TC levels measured during the early stage of stroke and the long-term functional outcome, as cholesterol levels in the HTC patients will decrease after initiating statin therapy. We therefore believe that the significant association between high TC levels and better long-term motor recovery seen in the present study would hold even with statin use. In addition, this study only recruited stroke patients from a single medical center, which limits the applicability of our findings.

Conclusions

The present study showed that patients with higher serum TC levels have better long-term balance function after first-time ischemic stroke. Nevertheless, because the main purpose of this study was to identify early predictors for long-term balance function after stroke, we cannot conclude that maintaining high serum levels of TC after ischemic stroke will improve balance function. Further studies are needed to investigate the mechanisms underlying the association between TC levels and balance function after ischemic stroke.

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Conflict of Interest and Funding Disclosure

None.

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