Functional Outcome of Elderly Survivors of Ischemic Stroke: A Retrospective Study Comparing Non-Hypercholesterolemic and Hypercholesterolemic Patients

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ABSTRACT: **Background:** Total cholesterol is significantly associated with increased risk of ischemic stroke. Patients with ischemic stroke and high cholesterol levels may show better functional outcome after rehabilitation.

Objectives: To study the possible interrelations between hypercholesterolemia and functional outcome in elderly survivors of ischemic stroke.

Methods: We conducted a retrospective chart review study of consecutive patients (age ≥ 60 years) with acute stroke admitted to a geriatric rehabilitation ward in a university-affiliated hospital. The presence or absence of hypercholesterolemia was based on registry data positive for hypercholesterolemia, defined as total cholesterol ≥ 200 mg/dl (5.17 mmol/L). Functional outcome of patients with hypercholesterolemia (Hchol) and without (NHchol) was assessed by the Functional Independence Measurement scale (FIM™) at admission and discharge. Data were analyzed by *t*-test and chi-square test, as well as linear regression analysis.

Results: The complete data for 551 patients (age range 60–96 years) were available for final analysis; 26.7% were diagnosed as having hypercholesterolemia. Admission total FIM scores were significantly higher in patients with Hchol (72.1 ± 24.8) compared with NHchol patients (62.2 ± 24.7) ($P < 0.001$). A similar difference was found at discharge (Hchol 90.8 ± 27.9 vs. NHchol 79.7 ± 29.2, $P < 0.001$). However, total FIM change upon discharge was similar in both groups (18.7 ± 13.7 vs. 17.6 ± 13.7, $P = 0.4$). Regression analyses showed that high Mini Mental State Examination scores ($\beta = 0.13$, $P = 0.01$) and younger age ($\beta = -0.12$, $P = 0.02$) were associated with higher total FIM change scores upon discharge. Total cholesterol was not associated with better total FIM change on discharge ($\beta = -0.012$, $P = 0.82$).

Conclusions: Elderly survivors of stroke with Hchol who were admitted for rehabilitation showed higher admission and discharge FIM scores but similar functional FIM gains as compared to NHchol patients. High cholesterol levels may be useful in identifying older individuals with a better rehabilitation potential.

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KEY WORDS: cholesterol, elderly, functional outcome, ischemic stroke, rehabilitation

A nationwide Israeli study conducted in 2004 documented the high burden associated with acute stroke [1] and estimated that about 13,000 people are admitted annually due to acute stroke. A 5-year survey of survival after stroke in Israel did not find any association between cardiovascular risk factors and mortality [2], yet high total cholesterol levels were shown to increase the relative risk of mortality from ischemic stroke by 11% in an Israeli male population [3].

The interrelations between stroke and cholesterol are complex and contain several paradoxes. In subjects older than 75 years, being in the lowest quartile of cholesterol level is associated with increased mortality [4], and levels below 189 mg/dl have been suggested as an early sign of unidentified comorbidity or of a rapid functional decline [5]. In contrast to the well-established association of various lipids levels and coronary heart disease [6], the epidemiological evidence connecting lipid levels with increased risk of ischemic stroke is less clear. Some studies found increased risk of ischemic stroke associated with increased total cholesterol levels [7], while others failed to show a clear association [8]. Another intriguing aspect of the relationship between total cholesterol and stroke is the possible prognostic value of total cholesterol levels in the period following acute ischemic stroke. To date, only a few studies on the effect of total cholesterol on survival after stroke have been published and they yielded different results. Censori et al. [9] showed that total cholesterol levels were not associated with short-term outcome in terms of disability and death, while Dyker and colleagues [10] reported an inverse association between lower total cholesterol levels and 3-month, but not 30-day, total mortality. More recently it has been shown

FIM = Functional Independence Measurement
Hcol = hypercholesterolemia
NHchol = non-hypercholesterolemia

that high total cholesterol levels were associated with better prognosis in the early stage (first month) following ischemic stroke [11]. A 10-year follow-up study of ischemic stroke concluded that higher total cholesterol levels were associated with less severe stroke as well as with reduced mortality rates [12]. Moreover, compared to patients with normal cholesterol levels, those with high cholesterol levels in the first month following ischemic stroke had a 2.2-fold lower risk of death [11]. This last study evaluated the functional outcome of stroke patients with hypercholesterolemia and suggested that higher levels of cholesterol are associated with a better outcome in the early phase after ischemic stroke. However, that study comprised relatively young stroke patients (mean age < 63), reported function only one month following stroke, was not conducted in a rehabilitation setting and did not evaluate rehabilitation outcome in terms of a standardized functional score system. Therefore, the purpose of the present study was to investigate the possible relationship of hypercholesterolemia and functional outcome as evaluated by the Functional Independence Measure, controlling for the presence of some prevalent comorbidities characteristic of these patients. In accordance with previous studies, we hypothesized that ischemic stroke patients with high total cholesterol levels might show a better functional outcome as compared with non-hypercholesterolemic patients.

PATIENTS AND METHODS

The study included 603 consecutive patients with acute stroke. Patients were admitted to the department of geriatric rehabilitation over a 48-month period (1 January 2004 – 31 December 2007) after a short stay in the departments of internal medicine or neurology. Primary inclusion criteria included stable medical status, enabling active rehabilitation treatment. Patients aged 60 years or older, with length of stay in the rehabilitation ward of less than 7 days (assuming that the extent of rehabilitation in such a short period is limited), residual brain damage due to infection, trauma or surgery, and patients with space-occupying lesions or hemorrhagic stroke were excluded. Deceased patients (n=23) were also excluded due to incomplete data (e.g., FIM on discharge). Stroke was diagnosed on the basis of clinical presentation of acute onset of focal neurological signs. Computed tomography or magnetic resonance imaging scans were performed in all cases to confirm the presence and nature of ischemic stroke. The presence or absence of hypercholesterolemia (total cholesterol ≥ 200 mg/dl, 5.17 mmol/L) was based on registry data positive for hypercholesterolemia (ICD 9 code 272.0). This registry data-recording system did not allow analysis of cholesterol levels as continuous variables.

The presence of other relevant risk factors such as arterial hypertension, ischemic heart disease (manifested as stable or unstable anginal syndrome), atrial fibrillation, previous stroke and diabetes mellitus were established by the medical history obtained during an interview of patients and/or caregivers, and a complete physical examination, as well as by the use of medical file codes from the International Coding of Diseases, 9th Revision (ICD-9).

SETTING AND PROCEDURE

In this retrospective chart review study we evaluated the possible associations between cholesterol status in stroke patients and their functional outcomes at discharge. The geriatric rehabilitation department is a 36-bed unit. This ward uses an interdisciplinary team approach, whereby medical personnel (physicians; nurses; physical, occupational and speech therapists; social workers; and psychologists) meet twice a week to evaluate the status of each patient. During these meetings, treatment plans are established and monitored. The patients undergo, on average, 6 hours of physical therapy and 6 hours of occupational therapy a week, and additional rehabilitation treatment as needed. Each patient was evaluated twice (on admission and discharge) for level of disability, by the FIM scale [13]. This tool is widely used to rate patients' performances on 18 activities of daily living. Total FIM scores range between 18 (reflecting complete dependence in all functional skills) and 126 (reflecting complete independence in all functional skills). In addition we calculated motor FIM, which consists of the 13 motor items of this scale (without the cognitive FIM items). Motor FIM score therefore ranges between 13 (minimum) and 91 (maximum) points. We also calculated FIM gain (total and motor) and daily FIM gain (total and motor). All patients were also evaluated for their cognitive level by the Mini Mental State Examination [14].

DATA ANALYSIS

Comparisons between patients with and without hypercholesterolemia were performed for a list of clinical and functional measures using *t*-tests for continuous variables and chi-square tests for dichotomous variables. Multiple linear regression analysis was performed to assess the independent associations of serum cholesterol status and demographic and clinical characteristics with total functional outcome by motor, total and FIM gain scores at discharge and with change in total functional outcome between admission and discharge. A P value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS system for Windows, version 10.0.1.

RESULTS

The data of 603 consecutive patients (age range 60–96 years) admitted with acute stroke were available. Fifty-two patients were excluded due to age < 60 years, non-ischemic nature of stroke, ward stay < 7 days, or death. The remaining 551 patients with a recent acute ischemic stroke were included in the final analysis. The clinicodemographic characteristics of these

Table 1. Clinical and cognitive characteristics of patients

Variables	All patients	NHchol	Hchol	*P* value
Sample size, n (%)	551	404(73.3)	147(26.7)	
Age (yrs, mean ± SD)	74.6 ± 9.2	75.5 ± 9.3	72.1 ± 8.6	‹ 0.001*
Gender (male %)	58.40	60.90	51.70	0.05†
Length of stay (days, mean ± SD)	46.6 ± 26.8	47.6 ± 27.1	43.8 ± 25.8	0.1*
Diabetes (%)	38.80	34.90	49.70	0.002†
Hypertension (%)	67	62.40	79.60	‹ 0.001†
Ischemic heart disease (%)	30.90	31.20	29.90	0.7†
Atrial fibrillation (%)	16.20	18.10	10.90	0.04†
Previous stroke (%)	19.80	20.80	17	0.3†
MMSE score (mean ± SD)	22.4 ± 5.4	22.1 ± 5.6	23.0 ± 4.9	0.1*

*Based on two-tailed Student's *t*-test

†Based on chi-square test

NHchol = non-hypercholesterolemia, Hchol = hypercholesterolemia, MMSE = Mini Mental State Examination

Table 2. Functional characteristics of patients by total cholesterol

Variables	NHchol	Hchol	*P* value
Admission total FIM (mean ± SD)	62.2 ± 24.7	72.1 ± 24.8	‹ 0.001
Discharge total FIM (mean ± SD)	79.7 ± 29.2	90.8 ± 27.9	‹ 0.001
Change in total FIM (mean ± SD)	17.6 ± 13.7	18.7 ± 13.7	0.4
Admission motor FIM (mean ± SD)	39.9 ± 18.4	46.8 ± 19.0	‹ 0.001
Discharge motor FIM (mean ± SD)	55.9 ± 22.2	64.2 ± 21.9	‹ 0.001
Change in motor FIM (mean ± SD)	15.9±11.9	17.4±12.4	0.1

*Based on two-tailed Student's *t*-test

NHchol = non-hypercholesterolemia, Hchol = hypercholesterolemia, FIM = functional independence measurement

patients are shown in Table 1. Mean age was 74.6 ± 9.2 years and most (58.4%) of the patients were male. Only 26.7% of the patients were hypercholesterolemic. There was a statistically significant difference between patients with Hchol (n=147) and the remaining patients (n=404) by age ($P < 0.001$), male gender ($P = 0.05$), diabetes mellitus ($P = 0.002$), arterial hypertension ($P < 0.001$) and atrial fibrillation ($P = 0.04$) [Table 1].

Patients with Hchol had statistically significant higher total FIM scores at admission ($P < 0.001$) and discharge ($P < 0.001$) compared with NHchol. These patients also had statistically significant higher motor FIM scores on admission ($P < 0.001$) and discharge ($P < 0.001$) [Table 2]. However, there was no statistically significant difference between the NHchol and the Hchol group in total and motor FIM change [Table 2]. We also performed multiple linear regression analysis to test the net effect of predictors on total FIM and on change in total FIM at hospital discharge. The results show that a higher MMSE score ($\beta = 0.41$, $P < 0.001$) is a significantly predictive factor of higher total FIM scores at discharge, while high total cholesterol predicts a higher total FIM score at discharge ($\beta = 0.11$, $P = 0.02$) [Table 3].

MMSE = Mini Mental State Examination

Table 3. Analysis of factors predicting total FIM at discharge

Independent predictors	Beta	*P* value*
Total cholesterol	0.11	0.02
Age	-0.17	< 0.001
Gender	-0.006	0.89
Hypertension	0.054	0.23
Diabetes	-0.027	0.56
Atrial fibrillation	-0.02	0.75
Ischemic heart disease	0.027	0.55
Parkinson 's disease	-0.061	0.18
Previous stroke	0.022	0.62
MMSE score	0.41	< 0.001

*Based on multiple regression analysis

MMSE = Mini Mental State Examination

Table 4. Analysis of factors predicting total FIM change at discharge

Independent predictors	Beta	*P* value*
Total cholesterol	-0.012	0.82
Age	-0.12	0.02
Gender	0.064	0.22
Hypertension	0.038	0.46
Diabetes	-0.052	0.31
Atrial fibrillation	-0.058	0.26
Ischemic heart disease	0.031	0.54
Parkinson 's disease	-0.09	0.078
Previous stroke	-0.081	0.12
MMSE score	0.13	0.013

*Based on multiple regression analysis

MMSE = Mini Mental State Examination

As shown in Table 4, total FIM change was independently, and inversely, associated with age ($\beta = -0.12$, $P = 0.02$), while higher MMSE score ($\beta = 0.13$, $P < 0.013$) is a significantly predictive factor of higher total FIM change at discharge. Total cholesterol did not predict a higher FIM change at discharge ($\beta = -0.012$, $P = 0.82$).

DISCUSSION

The main finding of this study was that the overall functional outcome of elderly stroke survivors was better for hypercholesterolemic patients, compared with those who were not. Total and motor absolute scores at admission and discharge were higher in such patients. However, both motor and total

FIM gains were similar in the two groups. This association was independent of a large number of prognostic factors but remained dependent upon cognitive state and age, known to play a major prognostic role in stroke rehabilitation [15]. Overall, the present study of a sample of elderly patients extends the results of a previous study [11] conducted in a younger stroke population that suggested an association of high cholesterol with a better functional outcome.

There are a few possible explanations for an ameliorating effect of high total cholesterol on functional outcome. These may include the fact that high cholesterol is a marker of a better nutritional and general health condition [16] contributing to improved outcome. This is in accordance with previous studies on the decrease of total cholesterol levels during the acute phase of stroke [17,18], hence, reflecting stroke severity. We therefore suggest that high cholesterol in these patients, at least during their stay in an acute inpatient rehabilitation setting, should be considered a favorable positive biological marker. Another explanation for cholesterol's ameliorating effect is the protective effect exerted by cholesterol on cell membrane fluidity [19], the responsiveness to vasodilator stimuli [20], and the blunting of unfavorable effects of oxidative stress on cerebral tissue [21]. In addition, our patients with normal cholesterol were older (75.5 ± 9.3 vs. 72.1 ± 8.6 years) and were less likely to suffer from diabetes and hypertension, but more likely to have atrial fibrillation or a previous stroke. This suggests that normocholesterolemic elderly patients represent a more vulnerable population, and reflects the fact that in patients over age 70 the levels of total cholesterol tend to decrease [22], which is perhaps one of several physiological derangements. The results may raise the issue of secondary stroke prevention in the elderly by use of cholesterol-lowering agents. While it is clear that we need to reduce the risk of stroke recurrence by all available means, there is still concern regarding the effectiveness of such treatment [23] and a lack of evidence-based studies in this population, so that current recommendations and guidelines applying to younger patients who have had a stroke [24] are still questionable. Our results may hint that cholesterol-lowering treatment should be less aggressively instituted, if at all, in older stroke patients. However, due to the limitations of these preliminary results, caution should be applied when considering the option of withdrawing cholesterol-lowering treatment in this high-risk population. Interestingly, there was a higher proportion of atrial fibrillation in patients without hypercholesterolemia. A similar cholesterol and triglycerides paradox has been shown in patients with paroxysmal atrial fibrillation, and it has been suggested that low hypolipoproteinemia may affect atrial vulnerability and cause atrial fibrillation [25].

Possible limitations of our study are its retrospective nature and design, and the fact that it included only the survivors of acute ischemic stroke, which does not allow for the establishment of a cause-effect relationship between hypercholesterolemia and functional outcome. The cutoff line of 200 mg/dl for total cholesterol may be argued, although it is commonly used in clinical practice. Using cholesterol as a dichotomous variable makes it impossible to rule out that some patients classified as "normal cholesterol" may have very low levels associated with poor nutrition. In addition, despite a careful adjustment made for important confounders, still others could have been considered. In particular, the data did not allow analysis of cholesterol levels (or its sub-fractions) as continuous variables, and did not consider pre-stroke cholesterol status or a possible change in cholesterol over time. We also did not incorporate any data of cholesterol-lowering medications. Moreover, generalizability to other populations rather than elderly stroke patients may be limited. A validation study of registry data, including accuracy of source documents and the level of skill and care applied in abstracting data, was not performed. Finally, longitudinal follow-up data would contribute to a better understanding of the interrelations between cholesterol and function in later stages. Despite these limitations, the present study is advantageous in the sense that it comprised a large sample of patients, all of whom underwent a similar rehabilitation program in a dedicated ward designed to treat elderly stroke patients, thus decreasing any degree of selection bias and increasing the validity of the study.

We conclude that functional outcome in elderly survivors of acute ischemic stroke undergoing rehabilitation is slightly more favorable in hypercholesterolemic patients, independently of a large number of prognostic factors. High cholesterol levels might also be useful in identifying older individuals with a better rehabilitation potential. Further studies are needed to confirm our observation.

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