# Low cholesterol as a risk factor for primary intracerebral hemorrhage: A case–control study

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## Abstract

**Introduction:** An inverse association between serum cholesterol and the risk of hemorrhagic stroke has been noted in epidemiological studies. We performed a case–control study to assess the relationship between primary intracerebral hemorrhage (ICH) and low serum cholesterol. **Materials and Methods:** Prospectively recruited fully evaluated patients with ICH were compared with a control group based in a primary care practice, i.e. age- and sex-matched individuals attending the routine preventive health check-up. Low cholesterol was defined by the sex-specific lowest quintile of the population. **Results:** The proportion of ICH patients with low cholesterol was significantly higher than the controls (68% vs. 43%). Mean total cholesterol was also signficantly low in ICH patients compared with controls (177 mg/dL vs. 200 mg/dl; $P$-value = 0.0006). Low-density lipoprotein cholesterol (LDL-c) and triglycerides were also significantly low in ICH patients compared with controls. Mean LDL-C in the ICH patient group was 114 mg/dL, whereas it was 128.5 mg/dL in the control group ($P$-value = 0.016). There was no significant difference in the high-density lipoprotein (HDL) levels in both groups. In a subgroup analysis, both men and women in the ICH group had a significantly low mean cholesterol compared with the control group. Although lower mean cholesterol was seen in both young and older individuals in the ICH group than in controls, the difference was significant only in the older group (age >45 years). In multivariate analysis, presence of low cholesterol remained a significant predictor of hemorrhage. The odds ratio of low cholesterol in the hemorrhage cases was 2.75 (95% CI = 1.44–5.49) unadjusted and 2.15 (1.13–4.70) adjusted for age and hypertension. **Conclusions:** This study confirms an increased risk of primary ICH associated with low cholesterol both in men and women, especially in older individuals.

## Key Words

Case–control study, intracerebral hemorrhage, low cholesterol, risk factor

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## Introduction

The paradox of a high stroke incidence in populations with low serum cholesterol has been reported in population-based studies.[1] One likely explanation for this observation is an inverse relationship between hemorrhagic stroke and serum cholesterol.[2,3] In Asian societies, where plasma cholesterol levels are low, hemorrhagic stroke may form up to 30% of all strokes.[4] Although other factors probably also contribute to this high frequency of intracerebral hemorrhage (ICH), low cholesterol levels have been proposed as one explanation for the high incidence of ICH in these countries. In a population-based study from North-East India, hemorrhagic stroke was found in 32% of the cases.[5] Three major American studies have confirmed this association. The multiple Risk factor Intervention Trial (MRFIT)[6] and Honolulu Heart Study (HHS)[7] analyzed populations of middle-aged men (aged 35–68 years), while the Kaiser programme cohort[8] consisted of both men and women across a wider range of ages (40–89 years). Other cohorts in Scandinavian and American populations demonstrated an association of low cholesterol with ICH in both sexes over a wider range of ages.[9-12] Since the introduction of highly effective means of lowering serum cholesterol by use of statins, the potential importance of this relationship has increased. In order to define the relationship between primary ICH and low cholesterol, we prospectively recruited patients hospitalized with ICH in a case–control design.

## Materials and Methods

Eighty-five consecutive patients admitted to the Malabar Institute of Medical Sciences (MIMS) hospital with a diagnosis of primary ICH were screened for this study between January 2007 and June 2008. Primary ICH was defined as sudden onset of an acute neurological event with confirmation of acute

intraparenchymal ICH provided by computed tomography (CT) scanning or magnetic resonance imaging (MRI). CT and MRI findings were clearly distinguished from hemorrhagic transformation based on standard criteria. After initial review for exclusion criteria, 74 patients were enrolled. Patients were excluded because of secondary causes of hemorrhage such as antecedent trauma (3), central nervous system tumor (3), vascular malformation (2), excessive anticoagulation or coagulopathy (3). Each patient was evaluated with history and physical examination by a neurological inpatient service, routine laboratory testing and brain imaging.

The control group consisted of 74 individuals, age- and sex-matched to the patient group presenting to MIMS primary care clinic for routine health checkup during the same study period.

For ICH cases and controls, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured in serum by standard chemical methods and low-density lipoprotein cholesterol (LDL-c) calculated by the Friedwald formula. All lipid values are reported in mg/dL. All blood samples were obtained in fasting state within 48 h of admission.

The primary outcome measure established prior to the study and in keeping with the reported epidemiologic data was the proportion of cases and controls with total cholesterol below a threshold level. The low-cholesterol threshold was designated as sex-specific lowest population quintile, <189 mg/dL for men and <202 mg/dL for women.[7] The proportion of individuals with low cholesterol among hemorrhage cases and control group were compared using 2x2 tables with Fisher's exact test for significance. Mean cholesterol values for cases and controls was calculated and compared using unmatched t-tests. All significance tests were two-sided, with *P* <0.05 designated as significant unless otherwise stated. All confidence intervals (CI) were set at 95%. Multivariate logistic regression analysis was performed. Potential covariates examined were age (in 5-year intervals) and presence or absence of hypertension. All analysis was performed with SPSS software.

## Results

Of the 74 patients, 50 were males and 24 were females. Mean age was 59.7 ± 14 years. Twelve patients were below 45 years of age. Controls were matched individually by age (+1) and sex. Baseline characteristics of the patient group are shown in Table 1.

Fifteen patients (21%) in the ICH group were alcoholic and 26 patients (36%) were smokers. Five patients (7%) were taking statins.

**Table 1: Comparison of patients and controls, baseline characteristics**

|                            | ICH group | Control group | *P*-value |
|----------------------------|-----------|---------------|-----------|
| HTN, %                     | 76        | 43            | 0.001     |
| Diabetes, %                | 38        | 35            | 0.61      |
| Coronary artery disease, % | 12        | 6             | 0.26      |

ICH = Intracerebral hemorrhage

CT scan brain was performed in all patients. Thirty-six patients (49%) had a bleed in the basal ganglia and thalamic region, six had cerebellar hemorrhage, two had bleed involving only brainstem, 14 patients had a basal ganglia bleed with significant lobar component and 16 patients had a lobar hemorrhage.

A significantly increased proportion (68%) of hemorrhage cases had total cholesterol values in the sex-specific lowest population quintile. Lower cholesterol values (below 160 mg%) were found in 43% of the patients in the hemorrhage group and 10.2% of the control group (*P*-value = 0.000). Mean total cholesterol for the ICH patients were significantly low compared with the control group (177 mg/dL vs. 200 mg/dL; *P*-value = 0.0006). Mean LDL-c and triglycerides were also significantly low in the ICH group [Table 2]. In the subgroup analysis, both men and women in the ICH group had significantly low mean cholesterol compared with the control group. In a separate analysis of patient subgroups based on age, although lower mean cholesterol values were noted in patients less than 45 years of age in the ICH group, the difference was not significant compared with the control group. In ICH patients above 45 years of age, significantly low cholesterol was noted compared with the control group (178 mg/dL vs. 201 mg/dL; *P*-value = 0.003). There was no significant difference for HDL in mean analysis between cases and controls.

Multivariate analysis was performed to control for potential covariates of cholesterol such as age and hypertension. The presence of low cholesterol remained a significant predictor of hemorrhage. The odds ratio of low cholesterol in the hemorrhage cases was 2.75 (95% CI = 1.44–5.49) unadjusted and 2.15 (1.13–4.70) adjusting for age and hypertension.

Twenty-six patients (35%) died during the hospital stay, 44 patients showed improvement and three patients worsened and was transferred to another center.

## Discussion

Many facts prompted us to analyze relationship between lipids and ICH. An increased relative risk for ICH was observed in women with decreasing serum cholesterol levels, whereas in men, the risk function was U-shaped.[9] Low levels increased the odds for ICH 2.25-fold after the adjustment for age and apolipoprotein E (APOE) genotype.[13] This confirmed an increased risk of primary ICH associated with low cholesterol,

**Table 2: Serum cholesterol and risk of ICH**

|                                  | ICH group (Mean ± SD) | Control group (Mean ± SD) | *P*-value |
|----------------------------------|-----------------------|---------------------------|-----------|
| Total cholesterol                | 177 ± 39              | 200 ± 43                  | 0.0006    |
| LDL cholesterol                  | 114 ± 37              | 128 ± 38.3                | 0.0162    |
| Triglycerides                    | 84 ± 35.5             | 129 ± 69                  | 0.0001    |
| HDL cholesterol                  | 42 ± 12               | 46 ± 12.2                 | 0.06      |
| Total cholesterol in men         | 178 ± 36              | 197 ± 46                  | 0.024     |
| Total cholesterol in women       | 177 ± 42.8            | 208 ± 38.3                | 0.011     |
| Total cholesterol >45 years age  | 178 ± 39              | 201 ± 44.7                | 0.003     |
| Total cholesterol <45years age   | 169 ± 30              | 197 ± 38                  | 0.067     |

*All cholesterol values are in mg/dL; LDL = Low-density lipoprotein; HDL = high-density lipoprotein; ICH = Intracerebral hemorrhage

specifically for hemorrhage due to hypertensive vasculopathy. Low serum cholesterol has been reported as an independent predictor for ICH in men,[14] elderly men[6] and men with serum cholesterol in the lowest quintile.[8]

Our data in patients with well-characterized primary ICH confirm the population-based observation that individuals with lowest cholesterol levels are at an increased risk of ICH. We found ICH to be associated with a significant overrepresentation below a threshold lipid concentration relative to the control group. We also observed a significantly lower mean cholesterol level in patients with ICH compared with the control group. Difference in mean cholesterol was significant in both men and women in our study. Although mean cholesterol was significantly low in both young and elderly individuals, the difference was statistically significant in individuals above 45 years of age. In the largest population-based study MRFIT, the mean cholesterol level in the hemorrhage and nonhemorrhage groups was 211 ± 44 and 214 ± 40, respectively, with a pronounced increase in hemorrhage only among those with cholesterol <160. The HHS and Kaiser cohorts similarly emphasized differences in proportion below a threshold rather than in mean cholesterol levels.

Corroborating previous findings examining ICH and cholesterol, we observed a moderate inverse association between LDL-c and ICH. Triglyceride levels were also inversely associated with ICH. Cholesterol and triglycerides play important roles in the cell membrane. There is increased erythrocyte fragility and decreased platelet aggregability *in vitro* and *in vivo* with reduced levels of cholesterol. It has been proposed that lower cholesterol results in a weakened endothelium that more readily leads to arterial fragility, hemorrhages or slower repair after small hemorrhages.[15,16] Potentially weakened endothelium may be more susceptible to microaneurysms, the chief pathological finding of cerebral hemorrhages. It remains unclear whether low cholesterol directly promotes ICH by these or other mechanisms. It is perhaps equally likely that the relationship might be based on a common underlying factor rather than a direct causal link.

A different impact of cholesterol, according to the stroke subtype, has also been described with an association between low serum cholesterol and the risk of ICH. A neuroradiological study demonstrated that the multifocal signal loss lesions on T2-weighted gradient echo MRI, which are microbleeds, are histopathologically related to mean concentrations of total cholesterol and LDL-c. Cholesterol and lipid levels were lower in patients with a severe degree of multifocal signal loss lesions on T2-weighted gradient echo MRI than that in those without these lesions. This suggests that lipid profile levels associated with the severity of hypertension may be linked with cerebral microbleeds.

Another fact is the relationship reported in some community-based studies between low cholesterol levels and mortality due to ICH. Low serum cholesterol correlated with risk of death from ICH.[17,18] A systematic review of mortality from causes other than ischemic heart disease found that very low serum cholesterol concentration increased mortality from hemorrhagic stroke.[19]

A potential source of error in this study is the use of lipid values during the first 48 h after ICH. Cholesterol determinations within the first 48 h after MI are thought to be reliable.[20] Some studies carried out following stroke have shown cholesterol levels to decline in the first 24–48 h after stroke, with a nadir at 1–2 weeks and a return to baseline at 2–3 months.[21] The fall in cholesterol <48 h after ICH appears to occur somewhat earlier than in myocardial infarction or ischemic stroke.[21,12] The cause of the posthemorrhage drop in cholesterol has been attributed to a nonspecific increase in chatecholamines.

Further understanding of the relationship between serum lipids and primary ICH has implications for both prevention of ICH and the potential risks of lipid-lowering therapies. While aggressive programs to lower lipids are of proven benefit, further understanding of the link between extremely low cholesterol and primary ICH could bear on these strategies in the future.

## Acknowledgments

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