Low Cholesterol as a Risk Factor for Spontaneous Intracerebral Hemorrhage

Hawar Adnan Mykhan *, Nawfal Madhi Sheaheed ,**
Akram Mohammad Almahdawi ***

ABSTRACT:

BACKGROUND:
Epidemiological studies indicate a higher incidence of intracerebral hemorrhage among persons with low total serum cholesterol level.

OBJECTIVE:
To examine the prospective relationship of total serum cholesterol with a subsequent intracerebral hemorrhage in an Iraqi population sample.

PATIENTS AND METHODS:
A case-control study was performed to assess the relationship between spontaneous intracerebral hemorrhage (ICH) and low serum cholesterol. Eighty patients were admitted, from April 2007 to April 2008, to both Baghdad Teaching Hospital and Sulaimaniyah General Teaching Hospital with a diagnosis of spontaneous ICH. All the patients aged 50 or more years. After the initial review for exclusion criteria, 62 patients were enrolled. The other patients were excluded because of secondary causes of hemorrhages. Brain CT scan was done at the radiology department of both hospitals and read by radiologists. Fasting serum lipid profile was evaluated by the laboratory staff of the hospitals.

RESULTS:
It was noticed that the cholesterol values fall acutely after hemorrhage. Mean total cholesterol was significantly lower within 48 h (total cholesterol 1TC1) and 1-2 weeks (total cholesterol 2TC2) than in 3 months (total cholesterol 3TC3), following hemorrhage. In addition, no significant change between TC1 and TC2 groups was noticed, though TC1 values proved to be somewhat higher. A significantly increased proportion (42%) of hemorrhage cases had TC3 values that were in the sex specific lowest quintile of the control group (20%). Dividing the cases according to likely etiology demonstrated similar overrepresentations within the hypertensive and non-hypertensive subgroups.

CONCLUSION:
Our data in patients with proved spontaneous ICH confirm the population based observation that individuals with the lowest cholesterol levels are at increased risk of ICH.

KEY WORDS: intracerebral hemorrhage, cholesterol, hypertension

INTRODUCTION:

Intracerebral hemorrhage (ICH) accounts for 8-13% of all strokes and results from a wide spectrum of disorders.[1] ICH is more likely to result in death or major disability than ischemic stroke or subarachnoid hemorrhage.[2] Association between low cholesterol and mortality due to ICH was documented in several large population-based studies. Studies in Japanese populations initially indicated a high incidence of hemorrhagic stroke among those with the lowest cholesterol levels.[3-5] The Multiple Risk Factor Intervention Trial (MRFIT) [6] and the Honolulu Heart Study (HHS) [7] analyzed populations of middle-aged men (aged 35-68), while the Kaiser Program cohort [8] consisted of both men and women across a wider range of ages (40-89). Two other cohorts in Scandinavian populations demonstrated an association of low cholesterol with ICH in both sexes over a wider range of ages .[9,10] The three major American cohort studies [6-8] found no significant differences in mean cholesterol between individuals with and without ICH.

*Neurologist Sulaimaniya Teaching Hospital.
**Specialist Neurologist Baghdad Teaching Hospital.
**Professor of Neurology, President of the Iraqi Board of Neurology, Consultant Neurologist at Baghdad Teaching Hospital.

Association has been reported between cerebral amyloid angiopathy (CAA) and particular alleles of the apolipoprotein E gene.[11-13] A case-control study dividing ICH into lobar and basal ganglionic locations showed low cholesterol in both groups.[14] In the large population-based cohort studies, information on etiology of ICH is generally unavailable. Even the question of whether the association between low cholesterol and ICH applies to hypertensive or normotensive individuals has given conflicting results.[6-9] In order to define the relationship between primary ICH and low cholesterol, we prospectively recruited patients hospitalized with ICH in a case-control design. We were thus able to characterize hemorrhages according to etiology using full clinical and imaging criteria.

PATIENTS AND METHODS:

A case-control study was performed to assess the relationship between spontaneous ICH and low serum cholesterol. Prospectively recruited and thoroughly evaluated patients with ICH were compared to an independent control group that was based in an outpatient care practice. Low cholesterol was defined by the sex specific lowest quintile of the outpatient care control (20th percentile < 190 for men and <200 for women).

Control Group: Hemorrhage cases were compared to an independent set of control patients. The outpatient care practice-based control group (OPC) consisted of 100 consecutive consenting individuals aged ≥ 50, who underwent routine physical examination in the outpatient clinics in Baghdad Teaching Hospital from January 2008 to April 2008. To minimize selection bias, prospective volunteers were not told that the research involved lipid testing until after they had willingly agreed to participate. Exclusion criteria for the control group were the following: History of dyslipidemia**,** previous history of ICH**,** Alcohol abuse**,** Patients with DM. **Determination of Lipids:** A pivotal point in analyzing lipid values following ICH is the possibility that they are affected acutely by the occurrence of hemorrhage. Based on these data, lipids in the hemorrhage cases were determined serially at the following intervals: within 48 h (Lipid 1)**,** 1-2 weeks (Lipid 2) **,** 3 months after onset of hemorrhage symptoms (Lipid 3). Unfortunately, 20 patients passed away during the research period; therefore, some lipid profile values could not be obtained. Lipids 1, 2 and 3 were obtained from 62, 58 and 42 cases, respectively. All lipid determinations were performed following a minimum of 12 h of fasting. Fasting lipid values were also obtained for the OPC control. For ICH cases and OPC control, total cholesterol (TC), high-density lipoprotein cholesterol (HDL), triglycerides (TG) and low-density lipoprotein cholesterol (LDL) were measured in serum by standard chemical methods. These lipid measurements were performed at the hospitals' laboratories. The primary outcome measure established prior to the study and in keeping with reported epidemiologic data, [15-17] was the proportion of cases and controls with TC below a threshold level. The low cholesterol threshold was designated as the sex-specific lowest quintile for the OPC control group. Individuals taking lipid-lowering agents (ICH n = 7 and OPC n = 24), were considered as falling above the lowest quintile in all analyses. Proportions of individuals with low cholesterol among hemorrhage cases and unmatched controls in the OPC group were compared using Fisher's exact test for significance. Multivariate logistic regression analysis was performed with the control group pooled. Potential covariates examined were age (in 5-year intervals), and presence or absence of HTN. Mean cholesterol values for cases and controls or for cases at various time points were calculated and compared using unmatched t-tests. Comparison of lipid values within an individual at sequential time points was performed using matched 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%. Data were collected and analyzed using SPSS version 10.0 for Windows.

RESULTS:

It was found that 48.38% of the patients have lobar and 51.62% have Capsular hemorrhage (Table 1). In (figure 1) we found that 63% of those who had lobar hemorrhage had low serum cholesterol while 69.35% of those with capsular hemorrhage had low serum cholesterol. We found that 66.13% of the 62 patients had low serum cholesterol within 48 hours, while 42% of the survived 42 patients had low serum cholesterol (Table 2 and figure 2). Mean total cholesterol was significantly lower within 48 hours (total cholesterol TC 1) and 1-2 weeks (total cholesterol TC2) than at 3 months (total cholesterol TC3) following hemorrhage ($p<0.01$). LDL cholesterol showed a similar decline to TC, measuring significantly lower at Lipid 1 than Lipid 3 ($p<0.05$), while TG showed a steady but non-significant increase from Lipid 1 to Lipids 2 and 3 (Table 3). Based on the decreased

cholesterol values observed at both of the first two time points, we restricted our analysis to those cases with determinations at least 3 months following ICH (Lipid 3). This constituted 42 of the initial 62 cases. Twenty patients died prior to their 3-month follow-up. We constricted our analysis to the survived patients with ICH after determination of their third reading lipid profile because it is presumed to be returned to the pre-hemorrhagic state. Basic comparison of the characteristics for the 42 patients with ICH and the control group (OPC) which is used in the final analysis is shown in (table 4). The OPC controls were younger than the hemorrhage group ($p < 0.001$). Their gender was roughly similar but we found that 56% of the control group had hypertension while 64% of the survived patients with ICH had hypertension ($p < 0.01$). The most significant result in our study was that the proportion of ICH cases with low cholesterol three months post-hemorrhage was significantly greater than that of the control group (42% vs. 20% in the control group, $p < 0.01$). Furthermore, low cholesterol increased the odds for hemorrhage 2.25-fold (1.12-4.50) after adjustment of age.These data confirm an increased risk for primary ICH associated with low serum cholesterol (Table 5).

Table 1: Relationship between number of patients and site of hemorrhage.

Site of Hemorrhage	No. Of Patients	%
Lobar	30	48.38%
Capsular	32	51.62%

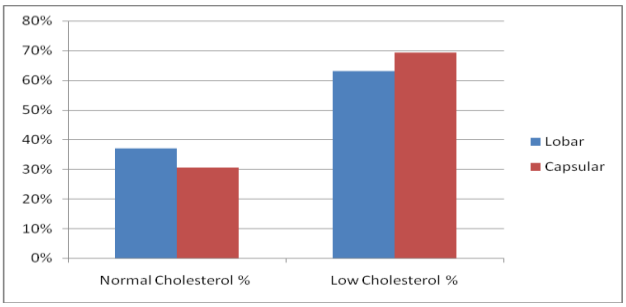

Figure 1: Relationship between site of hemorrhage and first reading serum cholesterol.

Table 2: Number of patients with normal and/or low cholesterol within 48 hours, after three months with percentage of survived patients whose serum cholesterol returned to normal after 3 months.

Serum Cholesterol	No. Of Patients with Normal Cholesterol	%	No. Of Patients with Low Cholesterol	%
TC1 In All Patients[1]	21	33.87%	41	66.13%
TC1 In Survived Patients[2]	21	50%	21	50%
TC3[3]	24	58%	18	42%

[1] Total No. of patients is 62. [2] No. of survived patients is 42. [3] In 8% of survived patients, serum cholesterol returned to normal.

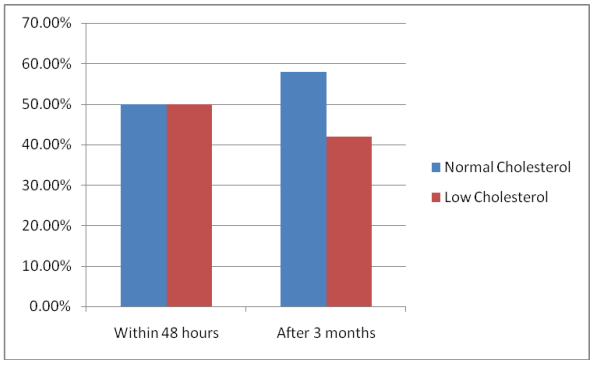

Figure 2: Percentage of survived patients whose serum cholesterol returned to normal after 3 months.

Table 3: Effect of acute hemorrhage on serum lipids.

	Lipid 1(within 48 h) mg/dl N=62	Lipid 2 (1-2 weeks) mg/dl N= 58	Lipid 3 (3 months) mg/dl N= 42
TC(total cholesterol)	180±20[a]	175±20[a]	217±25
LDL	115±20[b]	113±20	164±60[b]
HDL	42±9	40±9	48±7
TG(triglycerides)	95±50	130±48	140±59

All values are in mg/dl±SD.

[a] TC1(total cholesterol 1) and TC2 are significantly lower than TC3 ($p < 0.01$)

[b] LDL1 is significantly lower than LDL3 ($p < 0.05$)

Table 4: Comparison between the control group and patients with ICH.

	Control Group (Outpatient Care)	Patients with ICH[a]
Number	100	42
Age, ±SD	57.5±7.5[b]	61.5±11.5
Gender, %male	52	56
Hypertension, %	56[c]	64

[a] Cases with lipid profile 3 months post-hemorrhage.

[b] $p < 0.001$ Control Group vs. Patients with ICH.

[c] $p < 0.01$ Control Group vs. Patients with ICH.

Table 5: Serum cholesterol at three months and risk of ICH (a comparison between serum cholesterol of the control group and patients with ICH).

	Total No.	No. of Patients with serum Cholesterol in lowest quintile	Percentage of Patients with serum Cholesterol in lowest quintile
Out Patient Clinic	100	20	20%
Survived Patients with ICH	42	18	42%[a]

[a] $P<0.01$ Survived Patients with ICH vs. Control Group (OPC).

DISCUSSION:

Our data in patients with proved spontaneous ICH confirm the population based observation that individuals with the lowest cholesterol levels are at increased risk of ICH. We found ICH to be associated with a significant overrepresentation below a threshold lipid concentration relative to an independent control group. The magnitude of this effect, an adjusted odds ratio of approximately 2.3, is comparable to that seen in the large population studies.[6-8] A difference in proportion of cases below a threshold cholesterol level (the primary outcome variable chosen at the study's outset) without a difference in means is consistent with prior population studies.[6-8] In the largest population study Multiple Risk Factor Intervention Trial (MRFIT), mean cholesterol levels in hemorrhage and non-hemorrhage groups were 211+/-44 and 214 +/- 40, respectively, with a pronounced increase in hemorrhage only among those with cholesterol less than 160 .[(6)] The Honolulu Heart Study (HHS) and Kaiser cohorts similarly emphasized differences in proportion below a threshold rather than in mean cholesterol levels .[(7,8)] The biological explanation for this threshold effect, as for the association between cholesterol and ICH in general, remains unknown. Low cholesterol has been reported to cause increased erythrocyte osmotic fragility [(18)] and decreased platelet aggregability[(19)]. 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 (currently unknown) common underlying factor rather than a direct causal link. A potential source of error in this study is the use of lipid values 3 months following ICH as estimates of the pre-hemorrhage levels. This follows the practice of previous studies of cholesterol as a risk factor for myocardial infarction and stroke [(20,22,23,25)] and published recommendations for such studies.[(4,5)] In one report, determinations taken at 3 months following myocardial infarction showed close correlation with samples taken up to 2 years prior to the event (r = 0.78).[(24)] Another potential spurious cause of low cholesterols in the follow-up period is decline in nutritional status post hemorrhage. Another source of bias in our study was the exclusion of patients without lipid at least 3 months post ICH, generally because of early death. The excluded patients tended to have lower cholesterol at early time points than patients with nonfatal hemorrhage, however, suggesting that their inclusion might have strengthened rather than weakened the association detected in this study. The data on the timing of cholesterol changes post-ICH may help clarify future studies of stroke and lipids. The fall in cholesterol less than 48 hours after ICH appears to occur somewhat earlier than in myocardial infarction [(20,21,22,24,25)] or ischemic stroke.[(23, 26, 27)] A previous study of cholesterol in a smaller group of ICH patients found TC to be lower at 1 week than within 48 h of hemorrhage. [25] The cause of the post hemorrhage drop in cholesterol is not known. In the case of myocardial infarction, it has been attributed to a nonspecific increase in catecholamine, also seen in other stressful events such as general surgery. [(25)] It is possible that an earlier or more pronounced catecholamine surge in ICH may lead to an earlier drop in cholesterol [(25)]Further understandings of the relationship between serum lipids and primary ICH have implications for both the prevention of ICH and the potential risks of lipid-lowering therapies. [(28,29)] While aggressive programs to lower lipids are of proven benefit,[(30)] further understanding of the link between extremely low cholesterol and particular kinds of ICH could bear on these strategies in the future.

REFERENCES:

1. Lees KR, Zivin JA, Ashwood T: NXY-059 for acute ischemic stroke. N Engl J Med 2006 Feb 9; 354: 588-600.
2. Viswanathan A, Chabriat H: Cerebral microhemorrhage. Stroke 2006 ; 37:550-5.
3. Lin CH, Shimizu Y, Kato H, Robertson TL, Furonaka H, Kodama K,et al: Cerebrovascular disease in a fixed population of Hiroshima and Nagasaki. Stroke 1984;15:653-60.
4. Szatrowski TP, Peterson AV, Shimizu Y, Prentice RL, Mason MW, FukunagaY, et al: Serum cholesterol, other risk factors and cardiovascular disease in a Japanese cohort. J Chron Dis 1984; 37:569-84.
5. Tanaka H, Ueda Y, Hayashi M, Date C, Baba T, Yamashita H, et al: Risk factors for cerebral hemorrhage and cerebral infarction in a Japanese rural community. Stroke 1982;13: 62-73.

6. Iso H, Jacobs DR, Wentworth D, Neaton JD, and Cohen JD: Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the Multiple Risk Factor Intervention Trial. N Engl J Med 1989:320:904-10.
7. Yano K, Reed DM, Maclean CJ: Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. Stroke 1989; 20:1460-1465. Iribarren C, Jacobs DR, Sadler M, Claxton AJ, Sidney S: Low total serum cholesterol and intracerebral hemorrhagic stroke: Is the association confined to elderly men? Stroke 1996; 27:1993-98.
8. Gatchev O, Rastam L, Lindberg G, Eklund GA, Isacsson SO: Subarachnoid hemorrhage, cerebral hemorrhage and serum cholesterol in men and women. Ann Epidemiol 1993;3: 403-9.
9. Lindenstrom E, Boysen G, Nyboe J: Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: The Copenhagen City Heart Study. Br Med J 1994; 309:11-15.
10. Greenberg SM, Briggs ME, Hyman BT, Kokoris GJ, Takis C, Kanter DS, et al: Apolipoprotein E e4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. Stroke 1996; 27:1333-37.
11. Prekumar DR, Cohen DL, Hedera P, Friedland RP, Kalaria RN: Apolipoprotein E (epsilon)4 alleles in cerebral amyloid angiopathy and cerebrovascular pathology associated with Alzheimer's disease. Am J Pathol 1996; 148: 2083-95.
12. Nicoll JA, Burnett C, Love S, Graham DI, Dewar D, Ironside JW, et al: High frequency of apolipoprotein E (epsilon)2 allele in hemorrhage due to cerebral amyloid angiopathy. Ann Neurol 1997; 41: 716-721.
13. Giroud M, Creisson E, Fayolle H, Andre N, Becker F, Martin D, et al: Risk factors for primary cerebral hemorrhage: A population based study - the Stroke Registry of Dijon. Neuroepidemiology 1995; 14: 20-26.
14. Greenberg SM, Finklestein SP, and Schaefer PR: Petechial hemorrhage accompanying lobar hemorrhages: Detection by gradient-echo MRI. Neurology 1996:46:1751-54.7auv
15. Nishihara T, Nagata K, and Tanaka S: Newly developed endoscopic instruments for the removal of intracerebral hematoma. Neurocrit Care 2005; 2: 67-74.
16. Hankey GJ, Hon C: Surgery for primary intracerebral hemorrhage: is it safe and effective? A systematic review of case series and randomized trials. Stroke 1997; 28:2126-32.
17. Auer LM, Deinsberger W, Niederkorn K, et al: Endoscopic surgery versus medical treatment for spontaneous intracerebral hematoma: a randomized study. J Neurosurg 1989; 70: 530-35.
18. Leira R, Davalos A, Silva Y: Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. Neurology 2004; 63: 461-67.
19. Mendez I, Hachinski V, Wolfe B: Serum lipids after stroke. Neurology 1987; 37:507-51 1.
20. Gore JM, Goldberg RJ, Matsumoto AS, Castelli WP, McNamara PM, Dalen JE: Validity of serum total cholesterol level obtained within 24 hours of acute myocardial infarction. Am J Cardiol 1984; 54:722-725.
21. Ryder RE, Hayes TM, Mulligan IP, Kingswood JC, Williams S, and Owens DR: How soon after myocardial infarction should plasma lipid values be assessed? Br Med J 1984;289:1651-53.
22. Rubies-Prat J, Joven J: How soon after myocardial infarction should plasma lipid values be assessed? Br Med J 1985; 290:470-71.
23. Hachinski V, Graffagnino C, Beaudry M, Bernier G, Buck C, Donner A, Spence D, Doig G, Wolfe BMJ: Lipids and stroke: A paradox resolved. Arch Neurol 1996; 53:303-308.
24. Sewdarsen M, Vythilingum S, Jialal I, Nadar R: Plasma lipids can be reliably assessed within 24 hours after acute myocardial infarction. Postgrad Med J 1988; 64:352-56.
25. Cohn JS, McNamara JR, Chaefer EJ: Lipoprotein cholesterol concentrations in the plasma of human subjects as measured in the fed and fasted states. Clin Chem 1988; 34:2456-59.
26. Measurements following acute ischemic stroke. Cerebrovasc Dis 1997;7:10-13.
27. Woo J, Lam CWK, Wong HY, Teoh R, and Nicholls MG: Acute and long-term changes in serum lipids after acute stroke. Stroke 1990; 21:1407-1411.
28. Puddey IB: Low serum cholesterol and the risk of cerebral hemorrhage. Atherosclerosis 1996; 119:16.

29. Law MR, Thompson SG, Wald NJ. Assessing possible hazards of reducing serum cholesterol. Br Med J 1994;308: 373-79.
30. The Scandinavian Simvastatin Survival Study Group (45): Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. Lancet 1994; 344:1383-89.