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Serum lipid profile spectrum and delayed cerebral ischemia following subarachnoid hemorrhage: Is there a relation?

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Abstract

Background: Serum lipid abnormalities are known to be important risk factors for vascular disorders. However, their role in delayed cerebral ischemia (DCI), the major cause of morbidity after subarachnoid hemorrhage (SAH) remains unclear. This study was an attempt to evaluate the spectrum of lipid profile changes in SAH compared to matched controls, and their relation with the occurrence of DCI.

Methods: Admission serum lipid profile levels were measured in patients of SAH and prospectively studied in relation to various factors and clinical development of DCI.

Results: Serum triglyceride (TG) levels were significantly lower among SAH patients compared to matched controls (mean [±standard deviation (SD)] mg/dL: 117.3 [±50.4] vs. 172.8 [±89.1], $P = 0.002$), probably because of energy consumption due to hypermetabolic response. Patients who developed DCI had significantly higher TG levels compared to those who did not develop DCI (mean [±SD] mg/dL: 142.1 [±56] vs. 111.9 [±54], $P = 0.05$). DCI was noted in 62% of patients with TG >150 mg/dL, compared to 22% among the rest ($P = 0.01$). Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and lipoprotein (a) neither showed a significant difference between SAH and controls and nor any significant association with DCI. Multivariate analysis using binary logistic regression adjusting for the effects of age, sex, systemic disease, World Federation of Neurosurgical Societies grade, Fisher grade, and clipping/coiling, revealed higher TG levels to have significant independent association with DCI ($P = 0.01$).

Conclusions: Higher serum TG levels appear to be significantly associated with DCI while other lipid parameters did not show any significant association. This may be due to their association with remnant cholesterol or free fatty acid-induced lipid peroxidation.

Key Words: Cholesterol, delayed cerebral ischemia, lipid, remnant cholesterol, subarachnoid hemorrhage, triglyceride

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INTRODUCTION

Subarachnoid hemorrhage (SAH) remains a serious disease with high morbidity and mortality, despite improvements in diagnostic modalities, better Intensive Care Unit (ICU) facilities, microsurgical, and endovascular advancements.[5,28] This is principally due to the occurrence of delayed cerebral ischemia (DCI) or vasospasm.[3,5] Though attempts have been made to elucidate the pathophysiology of DCI in relation to the breakdown products of blood in the subarachnoid space, imbalance between vasoconstrictor and vasodilator substances, the cause-effect relationship remains elusive because of the presence of a plethora of causative factors.[3]

Serum lipid abnormalities have been noted as important risk factors in a variety of vascular disorders such as coronary artery disease, ischemic stroke, and peripheral arterial disease.[18,21] The lipid profile includes total cholesterol (TC) and triglycerides (TGs), which are carried as lipoproteins, the smallest being high-density lipoprotein (HDL), medium sized low-density lipoprotein (LDL), and larger sized TG rich lipoproteins (chylomicron remnants, very LDLs, etc.). The cholesterol content of these are reported for clinical reasons, as HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), and remnant cholesterol in TG rich lipoproteins, with serum TG levels being marker of remnant cholesterol.[18] Though initial clinical emphasis was on elevated levels of LDL-C, followed by lower levels of HDL-C, later non-HDL-C and TG have also been given due consideration.[18,21] Recently, lipoprotein (a) (Lp(a)) has also been identified to be an independent pathogenic lipoprotein in several of these vascular disorders.[15] Many of their patho-mechanisms overlap with that of DCI following SAH. Nevertheless, their direct association with either the pathophysiology of SAH or the occurrence of DCI has not been reported much.

The present study was to evaluate the spectrum of lipid profile changes in SAH compared to matched controls, and their relation with the occurrence of DCI.

METHODS

All adult patients with spontaneous SAH reporting within 48 h of ictus to the neurosurgical emergency of the Post Graduate Institute of Medical Education and Research, Chandigarh, India were included in the study. Patients with known history of hyperlipidemia, renal or liver dysfunction were excluded.

The serum samples for lipid measurements were taken at the time of admission. TG, TC, and HDL-C were analyzed by enzymatic colorimetric assay using Hitachi 704 Analyzer (Roche Diagnostics, Indianapolis, USA). LDL-C was calculated from measured values of TG, TC, and HDL-C in mg/dL according to the Friedewald equation: "LDL-C = TC − HDL-C − TG/5". Non-HDL-C was calculated by subtracting HDL-C from TC.[11] Lp(a) was analyzed by latex immunoturbidimetry. In addition to being considered continuous variables, they were also classified as per the optimal value cut-offs of National Cholesterol Education Program - Adult Treatment Panel III [Table 1].[9] The tests were also performed on fasting 30 age and gender matched apparently healthy volunteers from the same community to arrive at a local control range.

SAH patients were assessed since admission using World Federation of Neurosurgical Societies (WFNS) grading.[26] All good grade patients (WFNS Grades I–III) underwent urgent computed tomography angiography (CTA). Poor grade patients (WFNS Grades III and IV) underwent CTA once they improved. Further decision on securing the ruptured aneurysm by surgical clipping or endovascular coiling was taken depending upon patients' preference and aneurysm characteristics. All patients were managed in ICU during the postocclusion period with the following protocol: Phenytoin 300 mg/day (enterally or IV), nimodipine 60 mg 4th hourly enterally, and fluids to maintain central venous pressure of 10–12 cm of saline. Hypertensive therapy was utilized, at times, to maintain blood pressure 30 mm Hg above baseline. Patients' demographic profile, comorbidities (inadequately treated or severe hypertension or diabetes mellitus), WFNS and Fisher *et al.*[10] grades and treatment details were noted in a prospective database and followed up.

Outcome

DCI or symptomatic vasospasm was implicated if there was occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least two points on the Glasgow Coma Scale (either on the total score or on one of its individual

Table 1: Descriptive analysis of lipid profiles in SAH patients and matched controls

	Optimal values (mg/dL)#	Mean (±SD) (mg/dL)		P
		SAH patients	Matched controls	
TC	<200	164.8 (±47)	176 (±36.3)	0.17
HDL-C	>40	43.6 (±15.3)	46.3 (±16.2)	0.40
Non-HDL-C	<130	120.7 (±42.1)	129.7 (±37.4)	0.28
LDL-C	<100	85.5 (±35.8)	94.7 (±31.7)	0.2
TG	<150	117.3 (±50.4)	172.8 (±89.1)	0.002*
Lp (a)	<30[20]	27.9 (±25.1)	27.1 (±23.1)	0.90

#NCEP ATP III,[9] *Statistically significant. SD: Standard deviation, SAH: Subarachnoid hemorrhage, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, TG: Triglyceride, Lp (a): Lipoprotein (a), TC: Total cholesterol

components [eye, motor on either side, verbal]),[33] not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, imaging of the brain, and appropriate laboratory studies. Those who had died or discontinued treatment before 7 days were excluded from DCI outcome analysis.

Statistical analysis

SPSS 21 software (IBM Corp., New York, USA) was used for the statistical analyses. Univariate analyses of continuous variables across binary categories were compared using the independent samples *t*-test. The bivariate relationship between two continuous variables was assessed using the Pearson correlation coefficient. Proportions were compared using Chi-square or Fisher's exact test wherever appropriate, and subgroup analyses were done using the Breslow–Day test of homogeneity of odds ratios. Two-sided significance tests were used throughout, and the significance level was kept at $P < 0.05$. Multivariate analyses were conducted using binary logistic regression with mandatory significance of the model coefficient being <0.05 for validity of outcome prediction after adjusting for known prognostic factors such as age, sex, serious systemic disease, WFNS grade, Fisher grade, and definitive treatment in relation to lipid parameters found significant in univariate analysis.

RESULTS

There was a total of 86 patients enrolled initially in our study. Out of these, samples from only 77, 73, and 75 patients could be properly analyzed for Lp(a), TG, and other cholesterol levels, respectively, due to technical issues of blood samples. Of the total 86 patients, 75 who were available under treatment at 7 days following ictus were included in the outcome analysis. Their ages were normally distributed ranging from 20 to 76 years. The mean age was 49 years, and there were 17 patients aged 60 years or more. There were 39 males and 36 females. Among the 75 patients analyzed, 67, 64, and 65 patients had Lp(a), TG, and other cholesterol levels, respectively.

Serum TG levels were found to be lower among SAH patients when compared to matched controls (mean [±standard deviation (SD)] mg/dL: 117.3 [±50.4] vs. 172.8 [±89.1]) and the same was statistically significant ($P = 0.002$). These levels were normally distributed as shown in Figure 1. The values of other components of lipid profile did not show a significant difference between SAH patients and corresponding matched controls [Table 1].

DCI developed in 22 out of 75 patients. Patients who developed DCI had significantly higher TG levels compared to those who did not develop DCI (mean [±SD] mg/dL: 142.1 [±56] vs. 111.9 [±54], $P = 0.05$).

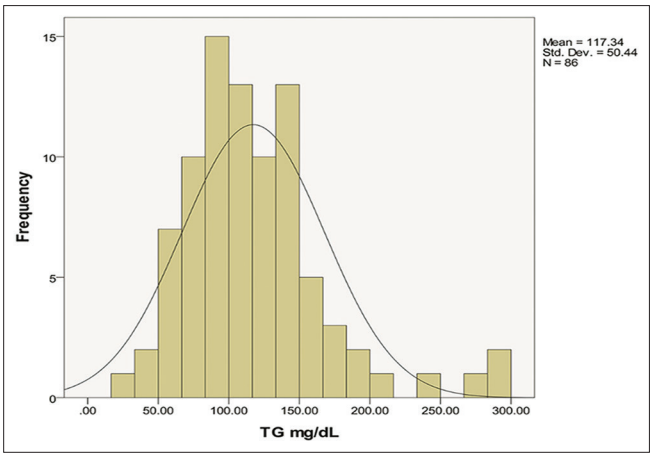

Figure 1: Distribution of triglyceride levels

DCI was noted in 8 out of 13 (62%) patients with TG >150 mg/dL, compared to 11 out of 51 (22%) among the rest ($P = 0.01$) [Table 2]. None of the other lipid components showed statistically significant association with DCI following SAH.

The difference in the occurrence of DCI in relation to TG levels in various subgroups is shown in Table 3. The impact of higher TG levels on DCI was homogeneous and did not show any significant subgroup difference.

The multivariate analysis using binary logistic regression adjusting for the effects of various factors on DCI is shown in Table 4. Higher serum TG levels and Fisher grades were noted to have a significant association with DCI, independent of age, sex, systemic disease, WFNS grade, clipping/coiling, and of each other. The independent effect of serum TG levels on DCI was both continuous, as well as categorical across the level of 150 mg/dL.

DISCUSSION

The variety of metabolic responses following the stress of SAH similar to traumatic brain injury is often strained further by pathophysiological challenges of compromised perfusion due to DCI.[3,5-8,28]

Though hyperlipidemia has been significantly implicated in several ischemic disorders, their association with SAH has been controversial.[19,22,29] In our study, serum TG levels were significantly lower at admission in patients with SAH compared to matched controls. While the same has been reported earlier, ascribing protective effect of high TG levels on the occurrence of SAH, larger prospective studies on communities and relatives of SAH patients have found no significant association of lipid levels with the occurrence of SAH.[22,29] This brings up the possibility of "reverse causality" due to the sampling time bias, in which lipid levels might not

Table 2: Relationship between serum lipid levels and DCI

	mg/dL	DCI			No DCI	
		n (%)	Categorical effect *P*	Mean (±SD) (mg/dL)	Mean (±SD) (mg/dL)	Continuous effect *P*
TC	<200	13/52 (25)	0.18	174.2 (±44)	158 (±49)	0.22
	≥200	6/13 (46.2)				
HDL-C	<40	9/30 (30)	0.9	42.2 (±18)	41.7 (±14)	0.92
	≥40	10/35 (28.6)				
Non-HDL-C	<130	11/41 (26.8)	0.58	132 (±36)	115 (±45)	0.15
	≥130	8/24 (33.3)				
LDL-C	<100	12/43 (27.9)	0.74	86.1 (±32)	80.9 (±37)	0.59
	≥100	7/22 (31.8)				
TG	<150	11/51 (21.6)	0.01*	142.1 (±56)	111.9 (±54)	0.05*
	≥150	8/13 (61.5)				
Lp(a)	≤30	15/52 (28.8)	0.76	26.8 (±22)	27.8 (±28)	0.9
	>30	5/15 (33.3)				

*Statistically significant. DCI: Delayed cerebral ischemia, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, TG: Triglyceride, Lp (a): Lipoprotein (a), SD: Standard deviation, TC: Total cholesterol

Table 3: Subgroup analysis showing occurrence of DCI in relation to TG levels by known prognostic factors

Subgroups	DCI (%)				
	Total	Subgroup versus DCI *P*	Effect of TG levels		
			<150 mg/dL	≥150 mg/dL	Subgroup difference *P*
Age in years					
<60	18/58 (31)	0.76	11/42 (26)	5/9 (56)	0.08
≥60	4/17 (24)		0/9 (0)	3/4 (75)	
Gender					
Female	14/36 (39)	0.08	6/23 (26)	6/7 (86)	0.18
Male	8/39 (21)		5/28 (18)	2/6 (33)	
Serious systemic disease					
−	14/47 (30)	0.91	7/33 (21)	5/7 (71)	0.47
+	8/28 (29)		4/18 (22)	3/6 (50)	
WFNS grade					
1-3	14/56 (25)	0.16	8/38 (21)	3/8 (38)	0.06
4, 5	8/19 (42)		3/13 (23)	5/5 (100)	
Fisher grade					
1, 2	1/3 (33)	1.00	0/1 (0)	0/0 (NA)	NA
3, 4	21/72 (29)		11/50 (22)	8/13 (62)	
Clipping/coiling					
+	19/66 (29)	0.72	11/48 (23)	5/9 (56)	0.25
−	3/9 (33)		0/3 (0)	3/4 (75)	

DCI: Delayed cerebral ischemia, TG: Triglyceride, WFNS: World Federation of Neurosurgical Societies, NA: Not available

influence the occurrence of SAH, but SAH may result in decreased TG levels as a result of consumption because of hypermetabolic stress response.[3,4] The mobilization of fat reserves for the needs of the metabolic response leading to fall in triceps skinfold measures has previously been reported.[4]

Though the impact of serum lipids on DCI may appear intuitive, and studies of cholesterol reducing agents (statins) in SAH are increasing,[13,14,30] there are hardly few studies directly relating serum lipid levels to DCI.[17,30] These studies surprisingly noted higher baseline LDL-C levels to have protective effect on DCI, contrary to the anticipated function of statins,[17,30] whereas an animal study noted cholesterol-fed rabbits to have greater degree of vasospasm following experimental SAH.[23] Studies in stroke revealed a similar paradox of the beneficial

Table 4: Multivariate effects of known prognostic factors on DCI

	Multivariate *P* value on DCI	
	Categorical effect	Continuous effect
Age	0.2	0.16
Sex	0.13	0.27
Serious systemic disease	0.4	0.84
WFNS grade	0.53	0.41
Fisher grade	1.0	0.02*
TG level	0.01*	0.01*
Clipping/coiling	0.71	0.24

*Statistically significant. DCI: Delayed cerebral ischemia, WFNS: World Federation of Neurosurgical Societies, TG: Triglyceride

effect of statins despite a weak association between cholesterol and stroke.[1] Though statins are definitely known to reduce LDL-C, their putative role in DCI may be due to their pleiotropic effects or impact on remnant cholesterol/TG.[12,25]

Among the lipid profile components, LDL, the main carrier of cholesterol to tissues became the prime focus for vascular disease prevention, which on entry into intima, undergoes oxidation and taken up by macrophages to kick start atherothrombosis.[21] HDL is involved in reverse cholesterol transport showing inverse association with vascular risk, albeit without much therapeutic utility.[20] Lp(a), an LDL like lipoprotein carrying more of oxidized phospholipids has also been noted to be associated with vascular diseases.[15] But none of these had much impact in our study.

Serum TG levels heretofore ignored has recently generated much evidence to be suggestive of remnant cholesterol in TG rich lipoproteins and more significantly associated with vascular diseases than others.[16,18] In this study, we noted higher serum TG levels to be significantly associated with DCI, independent of other known factors, both in continuous manner, as well as categorical across the level of 150 mg/dL. They may be markers of overall vascular risk. TG rich remnant particles (carrying 5–20 times cholesterol per particle than LDL) have been shown not only to traverse endothelium, but also cause inflammation and unregulated foam cell formation,[18,24,31] having stepwise association with all-cause mortality in contrast to LDL.[32] Free fatty acids (n = 6) released during lipolysis of TG induce lipid peroxidative injury.[2] Excess fat reserve or metabolic syndrome associated with elevated TG levels may also cause release of pro-inflammatory adipokines and/or endothelial dysfunction.[27] Higher skin-fold measures of adiposity have been noted to be significantly associated with vasospasm.[5]

The impact of serum TG levels indicating remnant cholesterol on the occurrence of DCI after SAH, as noted in this study has never been reported. The sample size of this study may appear small, but the potential for therapeutic modulation make it relevant. We need larger studies with complete categorization of all lipid parameters in relation to better outcome measures, so that we can fully validate the role of remnant cholesterol of TG rich lipoproteins in patients of SAH.

CONCLUSION

Higher serum TG levels at admission appear to be significantly associated with DCI following SAH, probably due to their association with remnant cholesterol or free fatty acid-induced lipid peroxidation, while other lipid parameters did not show significant association with DCI.

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Conflicts of interest
There are no conflicts of interest.

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