Effect of Aspirin on Lipoprotein(a) in Patients With Ischemic Stroke

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Hyperlipidemia and increased serum lipoprotein (Lp)(a) are independent risk factors for atherosclerosis and its complications. Serum Lp(a) concentration is not influenced by most lipid-lowering therapies other than niacin. Recently aspirin also has been reported to decrease its levels. In the current study, we evaluated the serum levels of Lp(a) and lipids in 25 patients with first-ever diagnosed ischemic stroke, aged 21 to 60 years, and compared their levels with an equal number of age- and sex-matched healthy control subjects. In addition, the effect of aspirin on Lp(a) levels was studied by estimating its levels after 4 weeks of daily treatment with 150 mg of aspirin. Both groups were comparable regarding their anthropometric measurements and routine laboratory parameters except that erythrocyte sedimentation rate was higher in the patients. Serum lipids were not significantly different between the two groups, although Lp(a) levels were significantly higher in the patients (27.40 ± 22.30 mg/dL) as compared with the control subjects (14.68 ± 11.75 mg/dL) ($P = .005$). Twenty of 25 patients (80%) had serum Lp(a) levels of more than 10 mg/dL, whereas only 11 of 25 control subjects (44%) had serum Lp(a) levels of more than 10 mg/dL ($P = .009$). After 4 weeks of treatment with aspirin, Lp(a) levels declined significantly (46.24%) from baseline 27.40 ± 22.30 mg/dL to 14.73 ± 10.47 mg/dL ($P < .001$). Patients with baseline levels greater than 25 mg/dL showed greater decline (55.63%) compared with those with levels less than 25 mg/dL (26.63%) ($P = .008$). Results of our study confirm that aspirin lowers the increased Lp(a) levels in patients with ischemic stroke. **Key Words:** Lipoprotein(a)—lipids—ischemic stroke—aspirin.

Focal ischemia or infarction of brain is usually caused by thrombosis of cerebral vessels themselves or by emboli from a proximal artery source or heart.[1] Hyperlipidemia is a strong risk factor for the development of atherosclerosis and its complications.[2] Lipoprotein (Lp)(a) is a low-density Lp (LDL)-like particle linked via a disulfide bond to an apo-Lp(a) polypeptide chain. Because of homology between apo-Lp(a) and plasminogen, Lp(a) has been hypothesized to act as a competitive inhibitor for plasminogen binding and, thus, inhibits endogenous fibrinolysis and, hence, contributes to thromboembolic disease.[3] It has been shown to be an independent risk factor for coronary heart disease (CHD).[3,4] Although it has now been shown that hyperlipidemia is an independent risk factor for stroke, the relationship between hyperlipidemia and stroke is not so strong as it is with CHD.[5] A number of cross-sectional studies have reported elevated Lp(a) levels in patients with stroke,[5-7] although few prospective studies have failed to show this association.[8,9]

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The serum level of Lp(a) is largely determined by genetic factors. Recently, high Lp(a) levels have been reported to be associated with higher incidence of ischemic stroke in blacks and white women but not in white men, further highlighting the importance of genetic factors in determining its level.[10] Except for high-dose niacin, few interventions decrease Lp(a) level.[11] In a recent study, beneficial effect of aspirin on Lp(a) levels was demonstrated.[12] In the current study, we evaluated the level of Lp(a) and other lipid parameters in patients with first-ever ischemic stroke. In addition, the effect of aspirin on Lp(a) level was studied by repeated estimation performed 4 weeks later.

Methods

The study was conducted at a tertiary care hospital in northern India. A total of 25 patients with ischemic stroke aged 21 to 60 years, who were brought to the medical emergency department, formed the study group. Another 25 healthy, age- and sex-matched, hospital workers or attendants of the patients formed the control group.

A patient was labeled as having ischemic stroke when that individual presented with acute onset of clinical signs of focal/global cerebral dysfunction and was documented to have cerebral ischemic infarction by computed tomography (CT) or magnetic resonance imaging (MRI) scan. The following categories of patients were excluded from the study: history of previous stroke, current nonischemic stroke, cardiac diseases predisposing to cardioembolic stroke, conditions causing dyslipidemia or altering Lp(a) levels such as diabetes mellitus, thyroid, liver, renal, or genetic lipid disorders, inflammatory or autoimmune diseases, malignancies, or disseminated intravascular coagulation, and receiving drugs such as statins, α- or β-blockers, and hormonal therapy, which may affect various lipid fractions. Only cigarette smokers who had not smoked for the past 3 months were included in the study. Informed consent was taken from all individuals enrolled in the study. A detailed history and physical examination was carried out. Various anthropometric parameters such as body mass index and waist-hip ratio were measured in both groups.

CT or MRI scan of brain was done in all cases. Routine investigations included complete blood cell counts, blood sugar, blood urea, serum creatinine, urinalysis, liver function tests, 12-lead electrocardiogram, and chest radiograph. Blood samples for lipids and Lp(a) estimation were collected within 24 to 48 hours of the onset of stroke and after at least 12 hours of fasting. The samples were centrifuged immediately, and an aliquot of plasma was obtained from each sample and stored at −70°C. Mannitol infusion for 3 to 4 days and aspirin (150 mg/day) administered orally or through nasogastric tube were given in all cases. No patient received thrombolytic or conventional lipid-lowering drugs. Serum Lp(a) level and other lipid parameters were repeated in all patients after 4 weeks. All investigations except CT or MRI scan of the brain were carried out in healthy control subjects as well.

Lp(a) levels were estimated by enzyme-linked immunosorbent assay technique using commercially available kits [Innotest Lp(a), Innogenetics, Ghent, Belgium]. A calibration curve was prepared using Lp(a) standards (0-80 mg/dL). Plasma levels of total cholesterol (TC), high-density Lp cholesterol (HDL-C), very LDL cholesterol (LDL-C), and triglyceride (TG) were measured using appropriate enzymatic methods. LDL-C was calculated using Friedwald, Levy, and Fredrickson formula.

Statistical Methods

Comparison of the Lp(a) levels between patient and control groups was done using Mann-Whitney U test. In patients with stroke, comparison of Lp(a) levels at baseline and after 4 weeks was done using Wilcoxon signed rank test. Prevalence of serum Lp(a) levels between two groups was compared using Pearson Chi square test. Comparison of lipid parameters was done using Student unpaired t test.

Results

There were 18 men and 7 women in each group. Mean age was 49.3 ± 7.7 years (range 30-60 years) in the two groups. There was no statistically significant difference between the two groups with regard to their anthropometric measurements and routine baseline laboratory investigations except that erythrocyte sedimentation rate was significantly higher in the patient group (Table 1). TC, LDL-C, and TG levels were slightly higher and HDL-C and very LDL-C levels were slightly lower in the patient group but none reached a statistically significant level. Baseline Lp(a) levels were significantly higher in the patient group (27.40 ± 22.30 mg/dL) as compared with the control group (14.68 ± 11.75 mg/dL, $P = .005$) (Fig 1). In patients with ischemic stroke, 20 of 25 (80%) had serum Lp(a) levels of 10 mg/dL or higher, whereas only 11 of 25 control subjects (44%) had serum Lp(a) levels of 10 mg/dL or higher ($P = .009$).

All patients with ischemic stroke received oral aspirin (150 mg/day). Repeated estimation of Lp(a) levels revealed a significant decline (46.24%) from the baseline level of 27.40 ± 22.30 mg/dL to 14.73 ± 10.47 mg/dL at 4 weeks ($P < .001$) (Fig 2). The decrease was greater in patients with Lp(a) level greater than 25 mg/dL. Patients with baseline Lp(a) levels greater than 25 mg/dL showed a greater decline (55.63%) in Lp(a) levels as compared with the patients with baseline Lp(a) levels less than 25 mg/dL (26.63%) ($P = .008$). Results of repeat estimation of other lipid parameters are shown in Table 2.

Table 1. *Anthropometric, baseline biochemical data and lipid profile in patients with ischemic stroke and healthy control subjects*

Variable	Patients (n = 25)	Control subjects (n = 25)	*P* value*
Hb, g/dL	11.94 ± 1.7	12.19 ± 1.6	.588
TLC, cells/mm^3	7980.0 ± 2061.8	7544.0 ± 1662.8	.415
ESR, mm in first hour	41.76 ± 10.6	34.04 ± 9.5	.009
Fasting blood sugar, mg/dL	108.92 ± 13.9	105.68 ± 10.8	.341
Blood urea, mg/dL	29.68 ± 7.0	27.64 ± 7.5	.505
Serum creatinine, mg/dL	1.02 ± 0.2	0.98 ± 0.2	.387
Body mass index, kg/m^2	26.65 ± 2.4	25.74 ± 2.5	.194
Waist-hip ratio	0.89 ± 0.04	0.87 ± 0.1	.192
TC, mg/dL	201.08 ± 45.6	190.72 ± 39.7	.401
LDL-C, mg/dL	134.84 ± 38.9	117.84 ± 26.6	.780
HDL-C, mg/dL	34.36 ± 6.8	37.36 ± 6.1	.107
VLDL-C, mg/dL	31.88 ± 15.6	35.52 ± 17.8	.446
TG, mg/dL	159.36 ± 38.0	117.64 ± 89.1	.444

All values are mean ± 1SD.

ESR, Erythrocyte sedimentation rate; *Hb,* hemoglobin; *HDL-C,* high-density lipoprotein cholesterol; *LDL-C,* low-density lipoprotein cholesterol; *TC,* total cholesterol; *TG,* triglycerides; *TLC,* total leukocyte count; *VLDL-C,* very LDL cholesterol.

*P value significant <.05.

Discussion

In this study, TC, LDL-C, HDL-C, and TG levels in patients with ischemic stroke were not significantly different from those of healthy control subjects, suggesting that the risk factors for symptomatic cerebrovascular disease may not be the same as in the general population. Our results are in accordance to the results of the Framingham Study[13] and Prospective Studies Collaboration Study[14] in which no direct relationship between ischemic stroke and TC level was observed.

At baseline, mean Lp(a) levels were significantly higher in the patient group, although there was wide variation in its levels in the two groups. In addition, levels greater than 30 mg/dL were found in significantly more patients as compared with control subjects (32% *v* 8%) (P = .034). Of patients, 80% had Lp(a) greater than 10 mg/dL, whereas only 44% of control subjects had Lp(a) levels greater than 10 mg/dL. This indicates that higher Lp(a) levels act as risk factor for ischemic stroke. Similar results were found in the Atherosclerosis Risk in Communities Study[15] and other studies.[6,16]

In our patients with ischemic stroke, serum Lp(a) levels showed 46.24% decline at 4 weeks. There are two possible explanations for this result. First, Lp(a) has been reported to increase in acute inflammatory conditions.[17,18] This increase has been hypothesized as a result of its increased rate of production in these conditions and it is accompanied by increase in levels of other acute phase reactants such as C-reactive protein, IL-6, and α1-antitrypsin. Because inflammatory process plays a key role in pathogen-

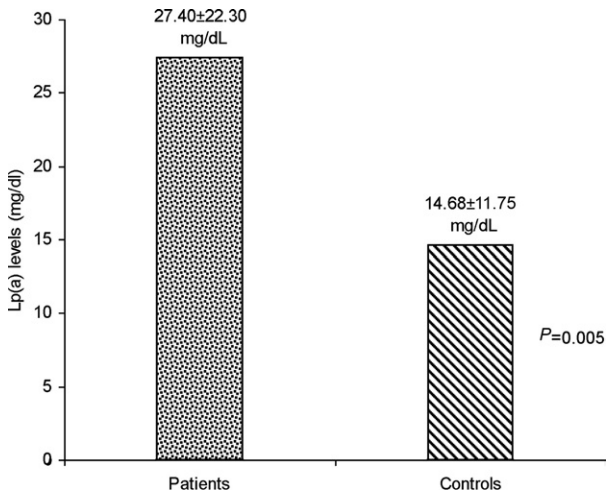

Figure 1. *Baseline lipoprotein(a) level in patients with ischemic stroke and healthy control subjects. *P value significant at <.05.*

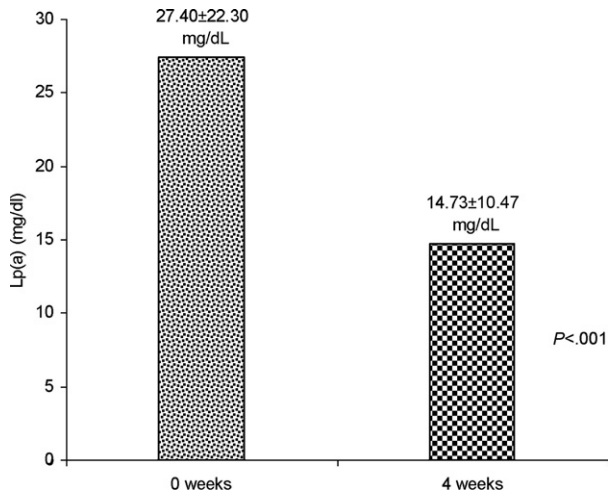

Figure 2. *Lipoprotein(a) levels in patients with ischemic stroke at 0 and 4 weeks after treatment with aspirin. *P value significant at <.05.*

Table 2. *Lipid parameters in patients with ischemic stroke at 0 and 4 weeks*

Variable	0 wk	4 wk	*P* value*
TC	201.08 ± 46.56	193.92 ± 41.57	.045
LDL-C	134.84 ± 38.90	125.32 ± 36.85	.006
HDL-C	34.36 ± 6.82	36.16 ± 4.8	.098
VLDL-C	31.88 ± 15.59	32.44 ± 16.58	.714
TG	159.39 ± 78.03	162.20 ± 82.88	.710

All values are mean ± 1SD.

HDL-C, High-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TC*, total cholesterol; *TG*, triglycerides; *VLDL-C*, very LDL cholesterol.

*P value significant $<.05$.

esis of atherosclerosis, it may result in elevation of Lp(a). In our study, erythrocyte sedimentation rate was higher among patients with stroke, which may signify underlying inflammatory process. However, most studies have reported a peak in Lp(a) levels after 8 to 10 days of onset of inflammatory conditions (i.e., longer than other acute phase reactants and a return to baseline after 4 weeks).[17,18] In addition, Craig and Ledue[19] did not find an acute elevation of serum Lp(a) levels similar to an acute phase response in patients with stroke. The Northern Manhattan Stroke Study showed that lipid and Lp(a) levels were not related to any change in acute phase protein and that there were no significant changes in mean serum lipids, apo-Lp, or Lp(a) levels during a 4-week period.[20] One study has shown its levels to increase and decline to baseline after about 21 days of stroke.[21] Because ischemic stroke has inflammatory component, Lp(a) along with other acute phase reactants may have a role in repair after tissue injury especially in process of angiogenesis.[18] In the current study, the baseline serum Lp(a) levels were estimated within 24 to 48 hours after the onset of stroke, hence, it is less likely that the higher basal levels of Lp(a) could have occurred so soon after the onset of stroke because of acute phase reactant response.

Although Lp(a) levels are genetically determined, recently it has been demonstrated that aspirin reduces its levels by decreasing apo-Lp(a) production from hepatocytes via suppression of transcriptional activity of apo-Lp(a) gene.[22] Moreover, platelet-specific alpha granules contain Lp(a), which may be released in plasma in association with platelet release reaction during platelet activation. Aspirin may inhibit the release of Lp(a) from these platelet granules by inhibiting platelet aggregation and release reaction. Lp(a) levels have been reported to decrease as much as 80% in patients with CHD and stroke after 1-month treatment with aspirin.[12] This has been the finding in our study as well. Because our patients also received aspirin throughout the study period, it is likely that aspirin may have been responsible for decline in its levels at 4 weeks in our study. This may reflect pleiotropic effect of aspirin on Lp(a) level.

To conclude, our study shows that Lp(a) may play a role in the pathogenesis of atherosclerosis in patients with ischemic stroke. The study also reveals that besides antiplatelet effects, aspirin has additional beneficial effect in decreasing the increased Lp(a) levels as early as 4 weeks especially in patients with markedly elevated Lp(a) levels.

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