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Original Article

Relook at lipoprotein (A): Independent risk factor of coronary artery disease in North Indian population



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ABSTRACT

Aims: Lipoprotein (a) [Lp(a)] levels have shown wide ethnic variations. Sparse data on mean Lp(a) levels, its link with clinical variables and severity of coronary artery disease (CAD) in North Indian population needed further studies.

Methods: 150 patients, each of single vessel disease (SVD), double vessel disease (DVD) and triple vessel disease (TVD) with 150 healthy controls were drawn for the study. Serum Lp(a) estimation was performed by immunoturbidimetric method.

Results: Lp(a) had a skewed distribution. Median Lp(a) level was significantly raised in cases as compared to controls (median 30.30 vs. 20 mg/dl, $p < 0.001$). Cases with acute coronary syndrome (ACS, 55.8%) had significantly higher median Lp(a) levels as compared to those with chronic stable angina (35.4 mg/dl vs. 23 mg/dl, $p < 0.001$). Significant difference in median Lp(a) levels were observed in patients with DVD or TVD versus control (30, 39.05 vs 20 mg/dl, $p < 0.008$). Lp(a) level was found to be an independent risk factor for CAD (AOR {adjusted odds ratio} 1.018, 95% CI 1.010–1.027; $p < 0.001$). Analysis using Lp(a) as categorical variable showed that progressive increase in Lp(a) concentration was associated with increased risk of CAD [AOR from lowest to highest quartile (1, 1.04, 1.43 and 2.65, p value for trend = 0.00026)]. Multivariably AOR of CAD for subjects with Lp(a) in the highest quartile (above 40 mg/dl) compared to those with Lp(a) ≤ 40 mg/dl was 2.308 (95% CI 1.465–3.636, $p < 0.001$).

Conclusion: Lp(a) above 40 mg/dl (corresponding to 75th percentile) assessed by an isoform insensitive assay is an independent risk factor for CAD. Raised Lp(a) level is also associated with increased risk of ACS and multivessel CAD.

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1. Introduction

Coronary artery disease (CAD) has become one of the major killers in developing countries including India. Conventional

risk factors have failed to explain the increasing burden of CAD, thus necessitating the need to search for newer risk factors like insulin resistance, thrombogenic factors, infection, inflammation and lipoprotein(a) [Lp(a)]. Lp(a) excess increase the risk of premature CAD 3–100 fold depending on the

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absence or presence of concomitant risk factors.^{1–4} Uninfluenced by age, sex, diet or environmental factors, Lp(a) values are genetically determined by Lp(a) gene located on chromosome 6q26-27 and stable lifelong levels are attained by age of two.^{4,5} Though earlier studies on relationship between Lp(a) and CAD had shown negative results,^{6,7} recently multiple studies have shown that elevated Lp(a) is independently and linearly predictive of future adverse coronary events.^{8,9} Lp(a) levels have shown worldwide ethnic variation with different levels associated with CAD in different populations. Data on levels of Lp(a) associated with risk of CAD from large North Indian population is still lacking, though there are few small studies to suggest its association with CAD.^{1,2,10–13} Thus this study was carried out to find out the level of Lp(a) independently associated with risk of CAD in the North Indian population (defined as Hindi speaking population residing from birth in the states of Delhi, Punjab, Haryana, Uttar Pradesh, Uttaranchal or Himachal Pradesh) and also its association with various clinical variables and conventional risk factors of CAD.

2. Materials & methods

This study is a prospective cross sectional case control study and was approved by the institutional ethical committee. Successive patients of CAD with unstable angina having TIMI risk score of 3 or higher¹⁴ and of chronic stable angina who were referred for coronary angiography were enrolled between January 2010 and June 2012. Selective coronary angiography was carried out using Judkin's technique in all patients. The right coronary artery was considered to be a single artery and the left coronary artery was subdivided into left anterior descending, circumflex and obtuse marginal branches. Observations of diagonals and other small vessel branches were not tabulated. Patients with left main disease were considered to be having double vessel disease. The arteries were judged by visual estimation to be normal, 50%, 75%, 90% and 100% obstructed, according to the maximum obstruction in any projection. According to the results of angiography, the patients were divided into three subgroups; single, double and triple vessel disease (disease defined by obstruction $\geq 50\%$). 150 patients each of single vessel disease (SVD), double vessel disease (DVD) and triple vessel disease (TVD) formed our study group of patients.

150 healthy, controls were selected from the attendants who were not first degree relatives of the patients. Presence of CAD in controls was ruled out by detailed clinical history, ECG, echocardiography and stress tests like treadmill test or dobutamine stress echocardiography if required. An informed consent was taken from all the subjects. Patients with history of recent ST elevation myocardial infarction (< 6 weeks), chronic liver and kidney disease, thyroid disorders, stroke, Familial hypercholesterolemia, acute/chronic infections and on therapy with sex hormones or anabolic steroids were excluded from the study. Fasting blood samples were drawn from all the participants of the study (cases and controls) 5 ml of venous blood was withdrawn and serum was immediately separated by centrifugation. The serum was stored at -70°C for subsequent analysis. Total cholesterol,

triglycerides and high-density lipoprotein cholesterol were estimated using commercial kits on Beckman CX4 auto-analyzer. Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula.¹⁵ Serum Lp(a) estimation was performed using quantitative Latex-enhanced Immunoturbidimetric test using human Lp(a) kit (Human Gessellschaft, Weisbaden, Germany). Strict external quality control using sera with known values was performed to validate the results.

3. Statistical analysis

Data has been expressed as mean $\pm$ SE for quantitative variables and as frequency (%) for qualitative variables. If quantitative variables followed normal distribution, unpaired students't test was used for comparing the data between two groups. In case of non-normal distribution, Mann Whitney U test was used to compare distribution between two groups and for more than two groups, Kruskal Wallis test was used. In case of multiple comparisons among the groups, the Bonferroni correction was applied. Statistical significance of categorical variables was determined by Chi-square test and Fisher's Exact test. Chi-square for trend was applied for unadjusted odds ratio and Likelihood ratio test (LRT) was used for testing trend for adjusted odds ratio (AOR) of Lp(a), when divided into quartiles. $p < 0.05$ was taken as a level of statistical significance. Univariate regression analysis was carried out using CAD as the dependant variable and age, sex, diabetes, hypertension, smoking, triglycerides, HDL cholesterol, LDL cholesterol, and Lp(a) as independent variables. Variables which showed an association with CAD ($p \leq 0.25$) in the univariate analysis were included as independent variables for multivariable logistic regression analysis. Statistical analysis was done using Microsoft excel and windows based SPSS version 16.0 (Chicago, IL). As one of the aim of a study was to assess the relationship of Lp(a) with severity of CAD, based on the study by Gupta et al¹¹ sample size calculated was a minimum of 95 subjects each of SVD, DVD, TVD and controls to have a power of 90% with 5% level of significance taking effect size 0.20 with pooled standard deviation of Lp(a) of 26. As Lp(a) has a skewed distribution further 10% was added to each group. Hence a minimum of 105 subjects were required in each group. As till date there has been no adequately powered trial to define the Lp(a) level associated with risk of CAD, we wanted to apply multivariable logistic regression to find the independent effect of Lp(a) on CAD. In our model, there were 14 independent risk factors including 3 dummy variables of Lp(a). As application of multivariable logistic regression requires a minimum of 10 subjects per variable (cases or control whichever is less) we decided to recruit 150 healthy subjects as controls and accordingly 150 patients each of SVD, DVD and TVD were enrolled.

4. Results

Descriptive statistics on study population is presented in Table 1. There was no significant difference in age [mean (SE) 53.4 ± 0.478 versus 52.34 ± 0.883 , $p = 0.15$] or sex ratio between

Table 1 – Baseline clinical characteristics and lipid profile of patients and controls.

Parameters	Cases (n = 450)	Controls (n = 150)	p value
Age ^a (years)	53.74 ± 0.478	52.34 ± 0.883	0.15
Sex (male/female)	363/87	127/23	0.273
BMI ^a (kg/m ²)	24.82 ± 0.191	24.47 ± 0.332	0.36
Diabetes mellitus n (%)	145 (32.2)	17 (11.3)	<0.001
Hypertension n (%)	209 (46.4)	61 (40)	0.218
Smoking n (%)	198 (44)	58 (38.6)	0.253
Family history of CAD n (%)	112 (25)	28 (18.7)	0.145
Chronic stable Angina n (%)	199 (44.2)	–	
Unstable Angina n (%)	251 (55.8)	–	
Total cholesterol (mg/dl)			
Mean ± S.E	138.5 ± 3.537	142.91 ± 4.599	
Median (IQR)	127 (108.7–152)	134 (115–155)	0.008
LDL cholesterol (mg/dl)			
Mean ± S.E	82.12 ± 3.454	73.59 ± 3.858	
Median (IQR)	68.2 (54.75–93.40)	65.3 (56–80.20)	0.84
Triglycerides (mg/dl)			
Mean ± S.E	151.1 ± 3.455	137.59 ± 4.476	
Median (IQR)	134.5 (100–179.25)	131.5 (92–162.75)	0.12
HDL cholesterol (mg/dl)			
Mean ± S.E	30.01 ± 0.361	32.69 ± 0.674	
Median (IQR)	30 (25–35)	32 (27–36.25)	0.001
Lp(a) (mg/dl)			
Mean ± S.E	41.11 ± 1.756	27.20 ± 1.705	<0.001
Median (IQR)	30.3 (14–55.92)	20 (12–40)	<0.001

BMI – Body Mass Index, CAD – Coronary Artery Disease, S. E – Standard Error, IQR – Interquartile Range.

^a Values are in mean ± S.E.

cases and controls (Table 1). There was also no significant difference between cases and controls with respect to conventional risk factors for CAD except that diabetes mellitus was present in higher number of cases compared to controls (32.2% versus 11.3% $p < 0.001$ Table 1). 55.8% of our patients had unstable angina at the time of presentation and rest had chronic stable angina. As majority of our patients were established cases of CAD, most of them were on standard doses of lipid lowering drugs [statins ($n = 403, 89.5\%$), fibrates (fenofibrate, $n = 84, 18.6\%$), ezetimibe ($n = 76, 16.8\%$)] but none were on niacin.

In our study population the various lipid components (total cholesterol, LDL cholesterol, HDL cholesterol triglycerides) and Lp (a) had a skewed distribution. So median along with interquartile range has been provided along with mean (SE). There was no significant difference in LDL cholesterol or triglyceride between cases or controls but HDL cholesterol was significantly lower in cases compared to controls (Table 1). The median Lp(a) level was significantly higher in cases compared to controls (30.3 mg/dl versus 20 mg/dl $p < 0.001$). The median Lp(a) levels showed a trend towards higher values with increasing severity of disease (Table 2) and Bonferroni pair comparison test showed a significant difference in Lp(a) levels between controls and patients with DVD or TVD and between patients with SVD and TVD (Table 2). The Lp(a) level

Table 2 – Lp(a) levels (mg/dl) in patients with CAD according to clinical presentation, angiographic severity and LDL levels.

Variable	Mean ± S.E (mg/dl)	Median (mg/dl)	IQR (mg/dl) ^a
Unstable Angina (n = 251)	45.5 ± 2.493	35.4 ¹	19–57.30
Stable Angina (n = 199)	35.5 ± 2.638	23.0	13–53
Single vessel disease (n = 150)	32.90 ± 2.265	23.00	11–50.25
Double vessel disease (n = 150)	40.22 ± 2.861	30.00 ²	15–55.55
Triple vessel disease (n = 150)	50.20 ± 3.68	39.05 ^{2,3}	16.5–66.2
LDL-C (<130 mg/dl) (n = 417)	39.69 ± 1.754	30 ⁴	14–54
LDL-C (>130 mg/dl) (n = 33)	59.03 ± 8.593	52.71	18.5–81.55

¹ $p < 0.001$ Unstable Angina versus stable Angina.

² $p < 0.008$ versus control [according to Bonferroni correction for multiple comparisons, p value less than (0.05/6) 0.008 is considered significant].

³ $p < 0.008$ versus single vessel disease.

⁴ Significant ($p = 0.02$).

^a Interquartile range.

was also significantly higher in patients with unstable angina compared to stable angina (Table 2). Age, sex, diabetes mellitus, hypertension, smoking, total cholesterol and triglyceride showed no significant influence on Lp(a) level (data not shown). However Lp(a) was significantly higher in cases with LDL cholesterol >130 mg/dl compared to those with LDL cholesterol <130 mg/dl (Table 2). Table 3 shows the results of regression analysis (univariable and multivariable) using CAD as a dependent variable. Univariate analysis showed diabetes mellitus ($p < 0.001$) HDL cholesterol ($p < 0.001$) triglyceride ($p = 0.04$) and Lp(a) ($p < 0.001$) were associated with CAD. In multivariable regression analysis, we included only risk factors which had a p value <0.25 in univariate analysis i.e. age ($p = 0.15$) hypertension ($p = 0.218$) LDL ($p = 0.197$) and also smoking ($p = 0.253$) as it was very close to cut off value of <0.25. Table 3 shows the results of multivariable regression analysis in which diabetes mellitus ($p = 0.001$) smoking ($p = 0.015$) HDL ($p < 0.001$) and Lp(a) ($p < 0.001$) showed an independent association with CAD. In this model, where Lp(a) was assessed as continuous variable, univariate analysis showed that 1 unit increase in Lp(a) increases the odds of CAD by 1.7%.and on multivariable analysis showed that the odds remained almost similar (1.8% increase per 1 unit increase in Lp(a), Table 3) suggesting that the risk due to Lp(a) is not confounded by other risk factors.

The risk of CAD was also assessed using it as a categorical variable. For this purpose Lp(a) was divided into quartiles based on its distribution in the control populations. The Lp(a) concentration showed a graded association with CAD. In the first quartile of Lp(a) (<12 mg/dl), 67.7% had CAD as compared to 68.5% in the 2nd quartile of 12–20 mg/dl, 74.5% in the 3rd quartile of 20–40 mg/dl and 83.4% in the 4th quartile (Trend $X^2 = 12.65$, $p < 0.001$, Fig. 1).

Table 4 shows odds ratio of risk for CAD for higher quartiles of Lp(a) compared to the first quartile taken as reference both unadjusted and multivariably adjusted for age, diabetes,

Table 3 – Univariable and multivariable regression analysis using CAD as dependent variable.

Variable	Univariable		Multivariable	
	OR (95% CI)	p value	AOR (95% CI)	p value
Age (years)	1.013 (0.995–1.031)	0.15	1.011 (0.992–1.030)	0.275
SEX	1.323 (0.801–2.186)	0.273	—	—
Diabetes mellitus	3.72 (2.163–6.396)	<0.001	4.019 (2.281–7.083)	<0.001
Hypertension	1.265 (0.870–1.841)	0.218	1.154 (0.762–1.747)	0.499
Smoking*	1.246 (0.854–1.818)	0.253	1.677 (1.105–2.544)	0.015
HDL cholesterol (mg/dl)	0.958 (0.936–0.981)	<0.001	0.955 (0.931–0.979)	<0.001
LDL cholesterol (mg/dl)	1.003 (0.999–1.007)	0.197	1.0 (0.996–1.005)	0.955
Triglycerides (mg/dl)	1.003 (1–1.006)	0.04	1.003 (1–1.006)	0.088
Lp(a) (mg/dl)	1.017 (1.009–1.025)	<0.001	1.018 (1.010–1.027)	<0.001

OR – odds ratio, AOR – adjusted odds ratio.

Risk factors which showed an association with CAD in univariate analysis, defined by p value ≤ 0.25 were included in analysis.

*Smoking was included as the p value was close to 0.25.

smoking, hypertension and various lipid parameters. In this model also, risk of CAD increased with increase in concentration of Lp(a) (p value for trend, 0.0026) but the odds ratio was statistically significant only in the highest quartile (OR 2.6 CI 1.530–4.684, $p = 0.001$) corresponding to Lp(a) value above 40 mg/dl compared to Lp(a) <12 mg/dl. Similarly, adjusted odds ratio for CAD achieved statistical significance only in the highest quartile compared to Lp(a) less than 20 mg/dl (50th percentile of our control population with odds ratio of 2.65 CI 1.622–4.330, $p < 0.001$, data not shown). We also analyzed the odds ratio of subjects with Lp(a) >40 mg/dl (i.e value above 75th percentile compared to those with Lp(a) ≤ 40 mg/dl and multivariably adjusted odds ratio of CAD was 2.308 (CI 1.465–3.636, $p < 0.001$). Hence in our study, subjects with Lp(a) above the 75th percentile had statistically significant increased risk of CAD compared to those with lower Lp(a) levels, suggesting that there is a threshold of Lp(a) concentration beyond which the risk of CAD increased significantly.

5. Discussion

Lp(a), a circulatory lipoprotein was discovered in 1963 by the Norwegian physician Kaare Berg¹⁶ and the year 2013 marks

the 50th year of its journey as a clinically relevant lipoprotein. Over the last 50 years, Lp(a) has evolved from an antigenic determinant in blood type to the strongest genetically determined risk factor for coronary artery disease.^{17–20}

Lp(a) is an LDL like particle which has apolipoprotein (a) attached to apolipoprotein (B) molecule via a disulphide bond. There are 34 different Lp(a) isoforms depending on the size of the apolipoprotein(a). This has resulted in significant variability in measured Lp(a) concentration if assays used are sensitive to variation in number of repeat domain in apo(a).^{21,22} Hence in 2003, an expert panel recommended use of assay systems not sensitive to apo(a) isoforms²³ and was accepted by World Health Organization (WHO) in 2003.²⁴ In our study, the kit used to assess Lp(a) level was isoform insensitive confirming to norms laid down by WHO. The rate of secretion by liver determines the Lp(a) levels. Apolipoprotein(a) has a close homology with plasminogen, which makes this molecule important not only in the process of atherosclerosis but also in thrombosis. While Lp(a) promotes atherosclerosis by increasing smooth cell proliferation and enhancing LDL-C retention in the subintima, it promotes thrombosis by competitively inhibiting plasminogen and upregulating expression of plasminogen activator inhibitor (PAI).²⁵

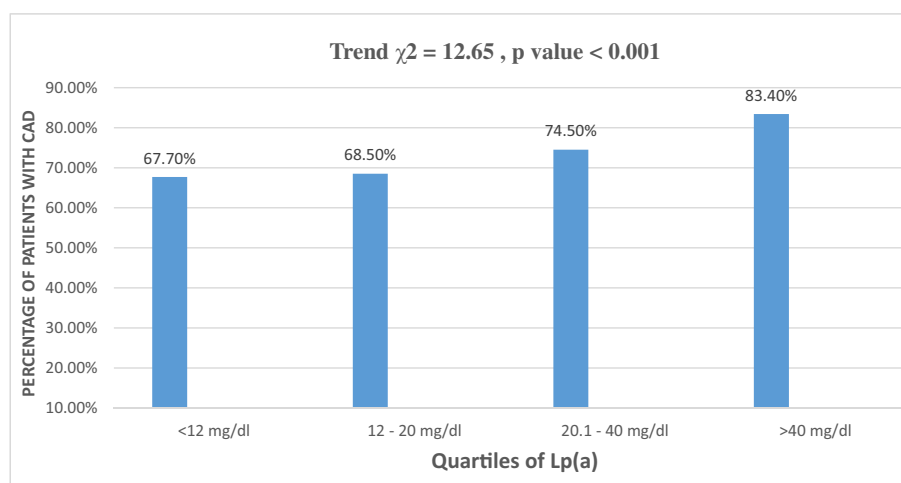


Fig. 1 – Percentage of patients with CAD according to quartiles of Lp(a) defined from control group.

Table 4 – Multivariable logistic regression expressing OR and 95% CIs for quartiles of Lp(a) whilst adjusting for age, diabetes, smoking, hypertension and lipid parameters (LDL cholesterol, HDL cholesterol and triglycerides).

Quartiles of Lp(a) (range, mg/dl) ^a				
	1 (<12)	2 (12–20)	3 (20.1–40)	4 (>40)
Cases (n)	88	74	117	171
Controls (n)	42	34	40	34
Unadjusted	1	1.039	1.396	2.4
OR (95% CI)		(0.601–1.796)	(0.835–2.334)	(1.427–4.038)
p value		0.892	0.203	<0.001
p value for trend = 0.0004				
Adjusted	1	1.040	1.432	2.652
OR (95% CI)		(0.583–1.855)	(0.831–2.469)	(1.520–4.629)
p value		0.894	0.196	0.001
p value for trend = 0.00026				

^a Quartiles were defined according to Lp(a) distribution in control population.

In our study, Lp(a) level showed a positive skewed distribution with a tail towards the highest levels (Fig. 2). This is in agreement with earlier studies conducted in the India.^{1,2,10–12} Vashisht et al²⁶ in 1992 were the first to demonstrate the presence of elevated Lp(a) in patients of CAD from North India. This was however a qualitative study which had shown that male patients aged less than 40 years, had three times higher incidences of detectable Lp(a) in comparison to control group. Since then, only few small studies have been conducted from North India which have shown the association of Lp(a) with CAD.^{1,2,10–13,27} The total numbers of patients enrolled in these studies were around seven hundred only and the methods used for assays were also different (Table 5). Hence, to draw definite conclusion about the median level of Lp(a) and its association with CAD, there was a need to study a larger population from North India by using a standard technique of Lp(a) estimation endorsed by WHO. In our study we found that Lp(a) level assessed by an isoform insensitive assay is an independent risk factor for CAD at a concentration above 40 mg/dl corresponding to the 75th

percentile of our control population. Our findings are in agreement with studies carried on the white population in Europe and USA reporting that only high Lp(a) concentration (corresponding to the top 20–25% of Lp(a) distribution) are associated with two to three fold increased risk of CAD.^{8,28–30} Accordingly the European Atherosclerosis Society Consensus Panel³¹ has defined Lp(a) level above the 80th percentile (corresponding to the 50 mg/dl) to be independently associated with increased risk of CAD. Our study is the first adequately powered study in the North Indian population to show that Lp(a) above the 75th percentile is an independent risk factor for CAD, similar to that proposed by the National Heart Lung and Blood Institute for North American Whites based on the Framingham Heart Study.²³

Hoogeveen RC et al²⁷ had proposed a cut off value of Lp(a) of >19 mg/dl on a study in 103 North Indian subjects (57 cases and 46 controls) based on the fact that 25% of the cases compared to 8% of controls in their study had Lp(a) in the highest quartile (>19 mg/dl). However in their study, Lp(a) protein was assessed by enzyme linked immunosorbant assay and value of Lp(a) mass was obtained indirectly by multiplying Lp(a) protein by conversion factor of 3.3. So indirect estimation of Lp(a) may have underestimated the true Lp(a) concentration. Gupta et al¹ had used the same isoform insensitive kit as ours to assess Lp(a) level in a small case control study (48 cases and 23 controls) in North Indian subjects of Jaipur. In that study, Lp(a) concentration of 20–30 mg/dl failed to show statically significant increased risk of CAD similar to our study. However they had not evaluated the risk of CAD at higher levels of Lp(a).

Rajasekhar et al,³ in a study from South India enrolling 151 patients have shown that Lp(a) >25 mg/dl is associated independently with around two fold risk of CAD. Larger studies from various part of the country (Eastern, Western and Central India) are needed to find out the level of Lp(a) associated with increased risk CAD as this will help in better risk stratification of subjects (with or without CAD) and its management. In our study, the median level of Lp(a) in the control group [20 mg/dl] is much higher than that reported among whites (6 mg/dl),

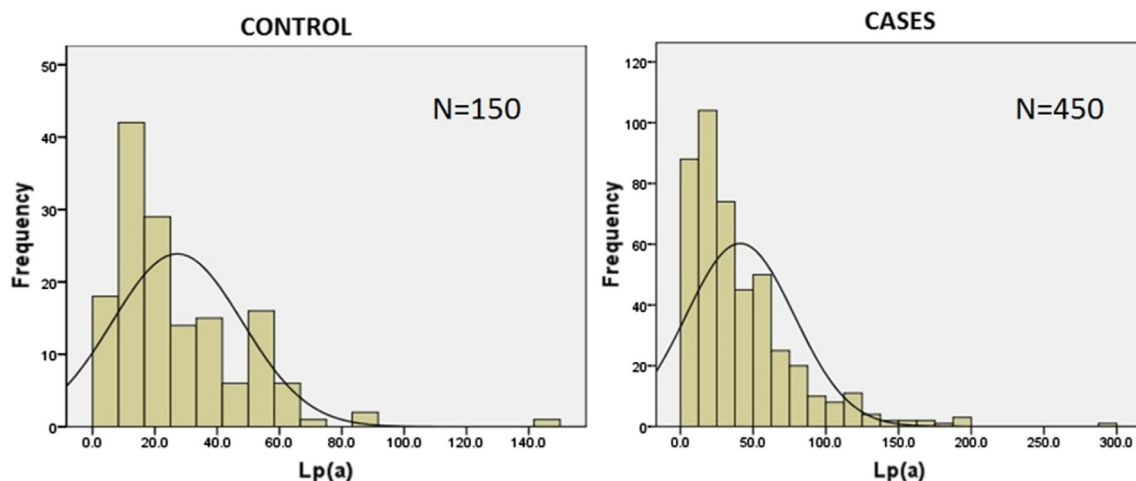


Fig. 2 – Histogram showing distribution of Lp(a) levels in controls and cases.

Table 5 – Studies of Lp(a) in North Indian population.

Study	No. of patients	Methods of Lp(a) estimation	Mean Lp(a) levels (mg/dl)
Present Study	450	Immunoturbidimetry	41.33 ± 38.46
Ashfaq F et al (2013) ¹³	270	Immunoturbidimetry	48.73 ± 23.85
Geethanjali et al (2003) ¹⁰	133	ELISA	41.90
Hoogeveen et al (2001) ²⁷	56	ELISA	12.65 ± 9.4
Gupta et al (2000) ¹	48	Immunoturbidimetry	11.95 ± 2.8 ^a
Gambhir et al (2000) ²	50	ELISA	35 ± 32.4
Vashisht et al (2000) ¹²	88	ELISA	40.90 ± 34.05
Gupta et al (1996) ¹¹	77	Immunoturbidimetry	83.83 ± 22.09 ^a

^a Geometric mean ± standard deviation.

American Indians (3 mg/dl)³² and Asian Indians residing abroad (16 mg/dl).³³

In our study, Lp(a) level was significantly higher in patients presenting with acute coronary syndrome as compared to those presenting with chronic stable angina ($p < 0.001$). Patients presenting with acute coronary syndrome comprised 55.8% of the total cases. Dangas et al³⁴ have shown that Lp(a) is distributed in larger amounts in the tissues from culprit lesions in the patients with unstable angina compared to those with stable angina. Stubbs et al³⁵ have also shown that Lp(a) is significantly higher in patients with non ST elevation myocardial infarction. Our study also support the role of Lp(a) in development of acute coronary syndrome justifying the hypothesis of Lp(a) producing prothrombotic state by competing with fibrin binding, inhibiting fibrinolysis and promoting platelet aggregation.

Zampoulkis et al,³⁶ studied the relationship of Lp(a) excess with the extent and severity of atherosclerosis in CAD patients and found that Lp(a) is related to diffuse lesions covering large part of coronary vasculature. Budde et al,³⁷ showed that Lp(a) levels correlated with the length of coronary lesions as well as the number of diseased vessels especially those with total occlusions. Similarly in our study, highest Lp(a) levels was observed in triple vessel disease followed by double vessel and single vessel disease and similar findings have been reported by Ashfaq et al¹³ and Gupta et al¹¹ on studies in North Indian population. This finding together with the finding of higher Lp(a) values in patients with acute coronary syndrome suggest the role of Lp(a) in pathogenesis of both atherosclerosis and thrombosis.

Low HDL cholesterol is an independent risk factor for CAD. In our study also, low HDL-C was found to be an independent risk factor for CAD which is in agreement with other Indians studies^{2,11,38} Most of our cases (89.5%, $n = 403$) were established cases of CAD and were receiving standard doses of lipid lowering drugs. Hence LDL-C and triglyceride levels were similar between cases and controls. In our study, Lp(a) level was significantly higher in patients with LDL cholesterol >130 mg/dl compared to those with LDL <130 mg/dl (median 52.71 mg/dl vs. 30 mg/dl, $p = 0.02$). This is due to the fact that LDL cholesterol calculated by Friedewald equation also includes the cholesterol carried in Lp(a).

Based on our data, we feel that apart from routine lipid profile, Lp(a) should be assessed in all patients of CAD. Statins, the wonder drug for managing dyslipidaemia along with fibrates and ezetimibe has unfortunately no effects on Lp(a) level.^{39,40} However niacin in dose of 2 g/day has been

shown to decrease Lp(a) by 25% and increase HDL by 40%⁴¹ though it was not effective in reducing clinical end points as reported recently.^{42,43} But to answer the question as to whether reduction of Lp(a) per se reduces risk of future adverse coronary events there is a need to develop a drug which selectively decreases Lp(a) only without effect on other lipid factors like LDL, HDL or TG. Selective reduction of Lp(a) only by lipid plasmapheresis has been shown to decrease risk of future adverse coronary events⁴⁴ and clinical development of specific Lp(a) lowering agents like Farnesoid X receptor agonists⁴⁵ will allow us to know the effect of selective Lp(a) reduction on future adverse cardiovascular events.

We also feel that Lp(a) should be routinely assessed in all our subjects with multiple risk factors for CAD (intermediate to high Framingham risk score) as has been recommended by The European Atherosclerosis Society³¹ and The National Lipid Association⁴⁶ to better predict the risk of developing CAD.

6. Limitation of study

We had enrolled only symptomatic patients of CAD referred for coronary angiography and had not included the entire spectrum of CAD patients. Hence the Lp(a) levels assessed in our study may not be representative of all patients with CAD. Secondly, majority of our patient were established cases of CAD on standard doses of lipid lowering drugs, which may have altered the association of lipids with CAD in the multi-variable regression analysis. However none of our patients were on niacin, which lowers Lp (a) levels.

7. Conclusion

This is the largest study till date from North India showing Lp(a) above 40 mg/dl assessed by an isoform insensitive assay is an independent risk factor for CAD. Raised Lp(a) level is also associated with increased risk of ACS and multivessel CAD.

Conflicts of interest

All authors have none to declare.

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