LIPOPROTEIN (A) : BETTER ASSESSOR OF CORONARY HEART DISEASE RISK IN SOUTH INDIAN POPULATION

D. Rajasekhar*, K.S.S.Saibaba**, P.V.L.N. Srinivasa Rao**, S.A.A. Latheef* and G. Subramanyam*

*Department of Cardiology, **Department of Biochemistry,
Sri Venkateswara Institute of Medical Sciences, Tirupati-517507, India

ABSTRACT

In an attempt to search for risk factors which can explain the increasing prevalence of coronary heart disease (CHD) in Indian population, we conducted a case-control study to assess the association of Lipoprotein (a)(Lp(a)) with CHD. One hundred and fifty one consecutive patients with clinical and angiographic evidence of CHD and forty-nine healthy controls were drawn for the study. Triglycerides, very low density cholesterol (VLDL-C), total cholesterol (total-C)/high density cholesterol (HDL-C) ratio, low density cholesterol (LDL-C)/HDL cholesterol ratio and Lp(a) were found to be higher in patients than controls. In female sex and in those with family history of CHD, higher total and LDL cholesterol levels were observed to be associated with higher Lp(a) levels. Lp(a) levels were also found to be higher in triple vessel disease than other vessel disease patients. Significant difference in Lp(a) levels were observed between normal coronaries vs. single and triple vessel disease ($P<0.05$) and also between single vs. double and triple vessel disease ($P<0.01$). Lp(a) levels correlated positively with vessel severity ($P<0.005$). Lp(a) levels >25 mg/dl were associated with coronary heart disease (Odds ratio 1.98 $P<0.05$ 95% CI 0.007-1.18). Our findings suggest a cut-off level of 25mg/dl for determination of risk of CHD. Studies from different areas involving larger sample size are needed to confirm the findings of the present study.

KEY WORDS

Lp(a), Coronary heart disease, vessel severity, risk factors, South Indian Population.

INTRODUCTION

Available evidence in literature has shown that Coronary Heart Disease (CHD) is progressively increasing in Indian population and projected to be the number one killer in the next decade (1). Traditional risk factors like smoking, hyper-tension, diabetes are reported to account for only 50% of prevalence and severity of the disease (2). This led to studies on newer risk factors like fibrinogen, Lp(a), homocysteine, tissue plasminogen activator etc. Studies on overseas Indians have shown that Lp(a) is an important risk factor for CHD. Studies on evidence of relationship between Lp(a) and CHD have shown discordant results but majority of the

studies show higher levels of Lp(a) in patients than in controls (3-5). Significant relationship of Lp(a) with CHD is reported in South Indian studies (6, 7). Lp(a) levels correlate with both early and advanced atherosclerosis, severity, extent and progression of atherosclerosis and all complications of CHD including re-stenosis following percutaneous transluminal angioplasty, stent and bypass surgery (5). Lp(a) excess increases the risk of premature CHD 3 to 100 fold depending on the absence or presence of concomitant risk factors (8). Indian population is undergoing epidemic transition as a result of affluence, urbanization and mechanization. Study of Lp(a) will help in the process of identifying the risk factors associated with the malignant nature of CHD in Indian population. Also measurement of Lp(a) levels in different populations can help in identifying the high risk group requiring aggressive pharmacological treatment (9, 10). Hence the present study was undertaken to find out the association of Lp(a) with CHD in Andhra population, a south Indian population.

Author for correspondence :

Dr. K.S.S. Saibaba
Additional Professor
Department of Biochemistry
Sri Venkateswara Institute of Medical Sciences
TIRUPATI-517507, Andhra Pradesh, INDIA
Email:ksssaibaba@yahoo.co.in

MATERIAL AND METHODS

Coronary heart disease patients (N=151) who attended the cardiology department, Sri Venkateswara Institute of Medical Sciences, Tirupati were recruited for the study based on clinical and angiographic evidence. An informed consent was taken from the patients. Patients with recent myocardial infarction (<6weeks), chronic liver and kidney disease and acute or chronic infections were not included in the study. Age of the patients ranged from 20-75 years (53.30 ± 9.12). Population based controls (N=49), normal symptomatically and electrocardiographically, were included in the study. Fasting blood samples were drawn from all the participants of the study.

Total cholesterol, triglycerides and high density lipoprotein cholesterol were estimated using commercial kits on Beckman Cx4 autoanalyzer. Low-density lipoprotein (LDL) cholesterol and very low density lipoprotein (VLDL) cholesterol were calculated using Friedewald's formula (11). Total cholesterol/HDL-C ratio and LDL-C/HDL-C ratio were calculated. Serum Lp(a) estimation was performed using quantitative latex-enhanced immunoturbidimetric test using Human Lp(a) kit (Human Gessellschaft, Weisbaden, Germany).

Statistical Analysis

All Continuous variables between patients and controls were compared using 't' test. One tailed 'p' values below 0.05 were considered significant. Discrete variable proportions were compared by Chi-square test. Lipid and Lp(a) values showed skewed distribution. Mann-Whitney U test was used to compare continuous variables between patients and controls. Pearson correlation coefficient was used to find out the relation between variables. Logistic regression was used to find out the association of dependent (CHD) and independent variable Lp(a), both dichotomized and the constant was included in the analysis. Statistical analyses were done using Microsoft Excel and windows based SPSS version 6.0.

RESULTS

Descriptive statistics on study population is presented in Table 1. Triglycerides, VLDL-C ($P<0.01$), Total-C/HDL-C ratio ($P<0.001$) and LDL-C/HDL-C ratio were found to be higher in patients when compared to controls. Higher percentage of low HDL-C ($<35\text{mg/dl}$) was observed in patients than in controls ($P<0.001$) (Table 1).

Significant difference in Lp(a) level was observed between patients and controls ($P<0.01$) (Table 1). In patients with CHD higher Lp(a) levels were

Table 1. Descriptive Statistics in Study population

Details	CHD patients N=151 Mean $\pm$ S.D.	Control N= 49 Mean $\pm$ S.D.
Age (years)	53.30 $\pm$ 9.12	48.71 $\pm$ 8.35
Male:Female ratio	130/21	28/21
Total-C (mg/dl)	179.55 $\pm$ 35.65	182.97 $\pm$ 37.85
Triglycerides (mg/dl)	142.88 $\pm$ 63.98	125.48 $\pm$ 64.06*
HDL-C (mg/dl)	35.37 $\pm$ 6.39	40.81 $\pm$ 5.43**
LDL-C (mg/dl)	114.20 $\pm$ 32.14	117.06 $\pm$ 32.68
VLDL-C (mg/dl)	28.45 $\pm$ 12.49	25.09 $\pm$ 12.81*
Total cholesterol/HDL-C ratio	5.19 $\pm$ 1.19	4.51 $\pm$ 0.87**
LDL-C/HDL-C ratio	3.30 $\pm$ 1.01	2.88 $\pm$ 0.78*
Smoking (%)	56 (37)	0 (0)
Diabetes (%)	71 (47)	0 (0)
Hypertension (%)	86 (57)	0 (0)
Family history of CHD	56 (37)	0 (0)
Hypercholesterolemia ($>240\text{ mg/dl}$)	11 (7)	5 (10)
HDL-C ($<35\text{ mg/dl}$)	77 (51)	4 (8)**
Lp(a) (mg/dl)	24.79 $\pm$ 18.99	16.04 $\pm$ 17.53*
*P<0.01 **P<0.001		

observed in female sex, family history of CHD, higher LDL cholesterol levels than males ($P<0.05$), no history of CHD ($P<0.01$) and normal LDL-C ($P<0.01$).

No significant difference in Lp(a) levels was observed with respect to age, diffuse disease, hypertension and angina respectively (table 2). Higher Lp(a) levels were observed in triple vessel disease than in normal coronaries ($P<0.05$), single vessel ($P<0.05$) and double vessel disease ($P<0.01$) (Table 3). Lp(a) showed significant positive correlation with vessel severity ($P<0.005$). Lp(a)

Table 2. Mean Lp (a) levels(mg/dl) in patients with CHD in different categories

Variable	Mean $\pm$ S.D
Males (N=128)	22.67 $\pm$ 18.77*
Females (N=23)	31.80 $\pm$ 19.31
<50 years (N=55)	21.38 $\pm$ 14.72
>50 years (N=96)	16.06 $\pm$ 8.26
Hypertensives (N=86)	25.76 $\pm$ 19.40
Normotensives (N=65)	23.14 $\pm$ 18.30
Family history of CHD (N=56)	29.11 $\pm$ 20.18**
No Family history of CHD (N=95)	20.30 $\pm$ 17.90
Hypercholesterolemia (>240 mg/dl) (N=11)	23.88 $\pm$ 6.19
Normocholesterolemia (N=140)	22.68 $\pm$ 18.54
HDL-C (<35mg/dl) (N=77)	20.48 $\pm$ 19.20
HDL-C (>35mg/dl) (N=74)	24.88 $\pm$ 17.85
LDL-C (<130 mg/dl) (N=104)	20.92 $\pm$ 17.68**
LDL-C (>130 mg/dl) (N=47)	28.10 $\pm$ 18.84
Focal vessel disease (N=75)	25.48 $\pm$ 18.30
Diffused vessel disease (N=51)	26.15 $\pm$ 20.63
Unstable Angina (N=62)	24.89 $\pm$ 18.60
Stable Angina (N=89)	24.70 $\pm$ 19.33
Type 2 diabetics (N=71)	24.27 $\pm$ 18.94
Non-diabetics (N=80)	25.05 $\pm$ 19.04
*P<0.05 **P<0.01	

levels >25 mg/dl were found to be associated with CHD (Odds ratio 1.98 95%, CI 0.007-1.18 P<0.05) in our study.

DISCUSSION

Low levels of total-C and HDL-C observed in patients when compared to controls in the present study is in agreement with the other Indian Study (12). Low levels of HDL-C are reported to increase

Table 3. Levels (mg/dl) of Lp(a) Vs vessel severity (Mean $\pm$ SD)

Variable	Single Vessel (N=51)	Double Vessel (N=21)	Triple Vessel (N=54)	Normal Coronaries (N=25)
Lp(a)	25.98 $\pm$ 19.80	15.90 $\pm$ 14.00	30.24 $\pm$ 19.38	18.00 $\pm$ 16.00

the risk of CHD even when total cholesterol is not elevated (3). With respect to low levels of HDL-C our study is similar to other studies (12-14). Increased total-C and LDL-C levels are reported in patients than in controls (13-16). In our study low levels of total-C and LDL-C were observed in patients against controls. This may be due to presence of lipid levels in controls in upper limit of normal range. Increased LDL-C/HDL-C ratio is reported in patients when compared to controls (13, 15). Similar observations were drawn in the present study.

Lp(a) is an LDL like particle which has apolipoprotein(a) attached to apolipoprotein B molecule via disulphide bond. There are 34 different Lp(a) isoforms depending on the size of the apo(a). Lp(a) levels are influenced by apo(a) polymorphism. Plasma Lp(a) levels are highly heritable. Stable life long levels are attained by age two. The rate of secretion by liver determines the Lp(a) levels. Ninety percent of the variation in plasma levels is accounted by the apo(a) gene and 70% by the size of apo(a) isoforms (17).

Mechanism of pathogenicity of Lp(a) excess include enhanced thrombogenesis and impaired fibrinolysis by competing with plasminogen, inhibition of transforming growth factor β , destabilization of plaque, increased smooth muscle cell proliferation and migration, formation of occlusive thrombus, impaired formation of collateral vessels, enhanced oxidation uptake and retention of LDL-C and upregulation of expression of the plasminogen activator inhibitor (PAI-I) (18-20).

Higher mean Lp(a) levels were observed in patients than controls and difference was statistically significant (P<0.01). This is in agreement with earlier studies conducted in India and abroad (3-5, 9, 15, 16, 22-34).

The distribution of Lp(a) levels showed skewed distribution in Chinese, Malays, Asian Indians, whites, blacks and Indians (3, 22, 35, 36). In the present study also distribution of Lp(a) levels showed skewness.

Among Asian Indians world wide the mean level of Lp(a) is 18-20 mg/dl. The median level is 16 mg/dl in Asian Indians, 22 mg/dl in blacks, 6 mg/dl in whites and 3 mg/dl among American Indians (38-40). In our study mean (24.79 mg/dl) and median (19 mg/dl) Lp(a) levels were both higher than in Asian Indians which may explain higher prevalence of CHD reported in South India (41).

Higher mean levels of Lp(a) were observed in cases than control in studies reported in India which ranged from 12 to 41mg/dl in patients and 8 to 24 mg/dl in healthy controls (3-5, 22-28). Mean Lp(a) levels in patients and controls in our study were within the range of values reported in earlier Indian studies. Mohan *et al.* (7) reported Geometric means for NIDDM (Non-insulin dependent diabetes mellitus) patients with or without CHD and controls as 24.6 mg/dl, 15.1 mg/dl and 19.4mg/dl and in the same study Lp(a) levels were higher in NIDDM patients with or without CHD than controls. In our study Geometric means for patients and controls were 15.65 mg/dl and 5.95 mg/dl respectively. Higher levels of Lp(a) were found in CHD patients with or without NIDDM against controls ($P<0.01$).

Pedreno *et al.* (30) showed no gender differences in Lp(a) levels in both patients and controls. Our study showed higher Lp(a) levels in females when compared to males in patients and is in agreement with other reports (32, 35, 42). Though influence of sex on Lp(a) is not established in literature and the higher levels of Lp(a) in females than in males may be due to lowering effect of testosterone in males (43) and presence of menopausal status (37) in women with CHD or may be due to discrepancy in sample size. Further studies are needed to confirm this observation.

Higher Lp(a) levels were reported in individuals with a strong family history of CHD than in those without such history ($P<0.01$) which is in agreement with other report (44). Lp(a) level is an important determinant of CHD among patients with familial and non-familial hypercholesterolemia (45). In the present study also higher Lp(a) levels were observed in patients with hypercholesterolemia than normocholesterolemia but not significant. The pathogenicity of Lp(a) is increased with high LDL and vice-versa (46-47). Lp(a) levels in our study were high in patients with LDL-C >130 mg/dl than patients having LDL-C <130 mg/dl($P<0.01$).

Higher levels of Lp(a) were reported in patients with unstable angina than stable angina (48). Our study observed no significant difference between patients with unstable and stable angina. Leonwattana *et al.* (49) observed 43.2% of unstable angina, 45.2% of stable angina patients and 28.8%

of controls showed Lp(a) >30 mg/dl. In the present study 32%, 34% and 22% of patients with unstable, stable angina and control showed Lp(a) levels >30 mg/dl.

Weak positive correlation of Lp(a) and systolic blood pressure and LDL-C was observed in one study (7). Other studies (8, 30) reported positive significant association of Lp(a) with LDL-C but Eritsland *et al.* (32) didn't observe correlation of Lp(a) with lipids. In the present study positive correlation of Lp(a) with LDL-C ($P<0.001$) was observed.

Lp(a) excess is the strongest determinant of angiographic severity and extent of CHD (49). Lp(a) levels correlate with the length of coronary lesions as well as the number of diseased vessels especially those with total occlusions (50). In our study also Lp(a) levels correlated positively with severity of atherosclerosis ($P<0.001$).

Higher Lp(a) levels were observed in triple vessel than single vessel disease but low Lp(a) levels were found in two vessel disease which may be due to small sample size compared to large variation as evidenced by standard deviation values. Significant difference in Lp(a) levels was observed with angiographic severity and extent of CHD in the present study. This finding is in agreement with other studies (4, 11, 52-56).

Lp(a) levels showed significant correlation with CHD in earlier studies (3, 7, 9, 16, 22, 52). Considering the Lp(a) levels in healthy population reported in Indian studies we have taken Lp(a) 25 mg/dl as cut-off value and analyzed its association with CHD using logistic regression and observed significant relationship (Odds ratio 1.98 95 CI% 0.007-1.18 $P<0.05$). Upper limits of normal Lp(a) are not defined in Indian population (3). In Caucasian population Lp(a) 30 mg/dl is considered as upper limit of normal. In Indian population Enas *et al.* (57) suggested Lp(a) 20 mg/dl as upper limits of normal Lp(a).

Our study confirmed positive correlation of Lp(a) with CHD at >25 mg/dl, a lower cut-off level in South Indian population for risk assessment than earlier studies (5). Lp(a) also showed positive association with angiographic severity. Higher median values of Lp(a) in the present study may explain higher prevalence of CHD reported in South Indian population. Females, patients with family history of CHD, hypercholesterolemia and with LDL-C >130 mg/dl showed higher Lp(a) levels. This finding indicates that these category of patients are at high risk of developing CHD in future as evidence shows that Lp(a) excess increases the risk of CHD in future depending on the absence

or presence of concomitant risk factors (7).

We examined whether total-C/HDL-C, which is considered as index of atherogenicity is related with CHD, but we didn't find association of total-C/HDL-C ratio with CHD. In the absence of association of total-C/HDL-C ratio and CHD, presence of higher levels of Lp(a) in patients indicates conventional risk factor like HDL-C, total-C may not be significant in causing CHD in South Indian population and higher Lp(a) may explain higher risk. This observation suggests that in addition to conventional lipid profile, estimation of Lp(a) can prove to be a valuable tool in risk assessment of population in general and management of disease in particular.

Our findings suggest a cut-off level of 25 mg/dl for Lp(a) to determine the risk of CHD. Studies from different areas involving larger sample size are needed to confirm the findings of the present study.

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