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Original Article

Others Section

To Assess Relationship of Lipoprotein (a) with Severity of Coronary Artery Disease in Patients with Acute Myocardial Infarction: A Hospital based Cross-sectional Study

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ABSTRACT

Introduction: Elevated plasma concentrations of lipoprotein {Lp(a)} have been consistently shown to be a risk factor for the development of a spectrum of thrombotic and atherosclerotic disorders including Coronary Artery Disease (CAD).

Aim: To assess relationship of Lp(a) with severity of CAD in patients of Acute Myocardial Infarction (AMI).

Materials and Methods: A hospital based, cross-sectional study was conducted at Topiwala National Medical College and B.Y.L. Nair Charitable Hospital, Mumbai, Maharashtra, India, between November 2016 to April 2018 (18 months). A total of 200 diagnosed cases of AMI who were willing to undergo coronary angiography were enrolled for this study. Prior to coronary angiography, a fasting blood sample was assessed for lipids and Lp(a) levels. The Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) score was calculated according to the coronary angiography results. Patients were divided into two groups based on Lp(a) levels: <25 mg/dL and >25 mg/dL and categorised based on CAD severity and SYNTAX scores as low (<22), intermediate (23-32) and high (>32). Lp(a) levels were categorised as low (<25 mg/dL) and high (>25 mg/dL). A p-value of <0.05 was considered as statistically significant. The statistical evaluation of data was done using the Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) program, version 20.0.

Results: Majority of the patients belonged to the age group 41-60 years. Males comprised 161 (80.5%) patients of the study population. Hypertension was the most prevalent risk factor, observed in 101 (50.5%) patients. Left ventricular ejection fraction <40% was observed in 85 (42.5%) patients. Majority had low SYNTAX score {92 (46%)}. There was a significant difference in patients with Lp(a) <25 mg/dL compared to patients with Lp(a) >25 mg/dL with low (45.7% vs. 54.3%, p-value=0.0001), intermediate (9.9% vs. 90.1%, p-value=0.0001) and high SYNTAX scores (10.8% vs. 89.2%, p-value=0.0001), respectively.

Conclusion: The Lp(a) was significantly associated with severity of CAD and it also displays prognostic significance.

Keywords: Atherosclerotic plaque, Coronary angiography, Creatine phosphokinase myocardial band, Troponin T

INTRODUCTION

Coronary Artery Disease (CAD) is a significant cause of morbidity and mortality in the developed and developing world. It is rapidly assuming epidemic proportions in developing countries [1]. India is one such developing country which is witnessing an epidemiological transition and thus on the threshold of suffering a cardiovascular disease epidemic [2]. Cause-specific mortality data highlight cardiovascular disease as a leading contributor of mortality [3]. Moreover, demographic data project a major increase in mortality attributable to cardiovascular disease parallel to increase in life expectancy and altering age structure of the growing population. Surveys performed in urban India reveal widespread prevalence of risk factors for CAD highlighting urgent action warranted to curb the spread of this disease as socio-economic development progresses [4-6].

Pathophysiology of CAD begins with the process of atherosclerosis. Atherosclerotic plaque is characteristic of a core formed of lipid surrounded by smooth muscle cells and foam cells (macrophages with lipids). The atherogenic dyslipidemia profile, especially mild to severe elevation of apo-B containing lipoproteins such as Very Low Density Lipoproteins (VLDL), VLDL remnants, Intermediate-Density Lipoproteins (IDL), Low Density Lipoproteins (LDL), and low levels of High Density Lipoproteins (HDL) appear to induce pronounced cholesterol deposition thus accelerating the progression of atherosclerotic disease within arteries [7].

Elevated plasma concentrations of lipoprotein (a)-Lp(a) is a risk factor that plays a role in the development of a spectrum of thrombotic and atherosclerotic disorders including CAD. However, mechanisms of Lp(a) that mediate the underlying pathophysiological effects are yet to be delineated. Atherosclerosis and thrombosis remain functionally bound due to the thrombotic events that ensue most often from rupture of an unstable atherosclerotic plaque, a common and significant manifestation of atherosclerotic disease. Lp(a) is capable of directly mediating functional linkage owing to its pro-atherogenic and prothrombotic effects. It displays a profound effect on endothelial function, perturbation of which has important ramifications for both atherogenesis and thrombosis. Hence, its capability to imbalance the pro and anticoagulant, pro and anti inflammatory, and vasorelaxation and vasoconstriction properties of the endothelium. Furthermore, it also plays a role in barrier function of the endothelium. Thus, Lp(a) constitutes a functional link not only between atherosclerosis and thrombosis, but also between endothelial dysfunction and both of these diseases [8]. These properties of Lp(a) warrant further studies of Lp(a) as a novel risk factor in patients with CAD. Against this background, this study aimed to evaluate Lp(a) as an independent risk factor for CAD in patients with AMI.

MATERIALS AND METHODS

This hospital based, cross-sectional study was performed at Topiwala National Medical College and B.Y.L. Nair Charitable Hospital, Mumbai, Maharashtra, India. A total of 200 patients

planned to undergo coronary angiography during the 18-month study duration from November 2016 to April 2018 were enrolled in this study. Study approval was obtained from the Institutional Ethics Committee (ECARP/2017/57). All patients provided written informed consent prior to study enrolment.

Inclusion and Exclusion criteria: Patients above the age of 18 years diagnosed with AMI based on electrocardiography and elevated cardiac markers such as troponin T and Creatine Phosphokinase Myocardial Band (CPK MB) were included in the study. Patients with thyroid disorders, renal failure (serum creatinine >1.5 mg/dL), nephrotic syndrome, sepsis, undergoing pregnancy, and terminally ill patients were excluded from the study.

Data Collection

Data for demographic details such as age, gender, cardiovascular risk factors, SYNTAX score, and lipid profile were collected. The study population was divided into two groups based on Lp(a) levels: <25 mg/dL and >25 mg/dL. This cut-off was determined based on another study revealing atherosclerotic cardiovascular disease onset at Lp(a) levels 20-30 mg/dL [9].

Angiographic Evaluation

Coronary angiography was performed using the Judkins technique. Severity of CAD was evaluated using the SYNTAX score [10] and was as categorised low (<22), intermediate (23-32) or high score (>32) on coronary angiography. The SYNTAX score was compared with Lp(a) levels to determine an association of Lp(a) with severity of CAD.

Laboratory Investigations

Fasting venous blood samples were obtained for all patients. These samples were evaluated for troponin T/I or Creatine Phosphokinase-Myocardial Band (CPKMB) levels, complete lipid profile (cholesterol, triglycerides, HDL, LDL, VLDL), Lp(a), random blood sugar, thyroid profile tests if clinically suggestive of thyroid disorder, haemoglobin, white blood cell count, platelets, total bilirubin, serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase, and serum creatinine.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±standard deviation and categorical variables as expressed as percentages. Categorical variables were compared using either Chi-square test. A p-value of <0.05 was considered as statistically significant. The statistical evaluation of data was done using the SPSS; Chicago, IL, USA program, version 20.0.

RESULTS

Demographics of study population: The study recruited 200 patients. Majority of the patients belonged to the age group 41-60 years. Males comprised 161 (80.5%) patients of the study population. Hypertension was the most prevalent risk factor, observed in 101 (50.5%) patients. Left ventricular ejection fraction <40% was observed in 85 (42.5%) patients. Majority had low SYNTAX score {92 (46%)}. Almost three-quarter patients i.e., 147 (73.5%) had high Lp(a) levels. Lipid profile of the study comprised of cholesterol >200 mg/dL reported in 25 (12.5%) patients, triglycerides >150 mg/dL in 48 (24%) patients, HDL >40 mg/dL in 110 (55%) patients, and LDL >200 mg/dL in 73 (36.5%) patients [Table/Fig-1].

Association between Lp(a) with severity of CAD: There was a significant difference in patients with Lp(a) <25 mg/dL compared to patients with Lp(a) >25 mg/dL with low (45.7% vs. 54.3%, p-value=0.0001), intermediate (9.9% vs. 90.1%, p-value=0.0001) and high SYNTAX scores (10.8% vs. 89.2%, p=0.0001), respectively [Table/Fig-2].

Variables	Patients n (%)
Age	
21-40 years	23 (11.5)
41-60 years	118 (59)
61-80 years	59 (29.5)
Gender	
Males	161 (80.5)
Female	39 (19.5)
Medical history	
Hypertension	101 (50.5)
Diabetes mellitus	73 (36.5)
Left ventricular ejection fraction	
<40%	85 (42.5)
40-49%	83 (41.5)
>49%	32 (16)
SYNTAX score	
Low (<22)	92 (46)
Intermediate (22-32)	71 (35.5)
High (>32)	37 (18.5)
Lipoprotein (a)	
Low (<25 mg/dL)	53 (26.5)
High (>25 mg/dL)	147 (73.5)
Cholesterol	
<200 mg/dL	175 (87.5)
>200 mg/dL	25 (12.5)
Triglycerides	
<150 mg/dL	152 (76)
>150 mg/dL	48 (24)
High density lipoprotein	
<40 mg/dL	90 (45)
>40 mg/dL	110 (55)
Low density lipoprotein	
<200 mg/dL	127 (63.5)
>200 mg/dL	73 (36.5)

[Table/Fig-1]: Demographics of study population.
Hypertension was defined as blood pressure ≥140/90 mmHg; patients n=200; Diabetes was defined as random blood sugar ≥126 mg/dL or glycated haemoglobin (HbA1C) ≥6.5%

Variables	Lipoprotein (a) <25 mg/dL	Lipoprotein (a) >25 mg/dL	p-value (Chi-square)
Age (years)			
<40	9/23 (39.1%)	14/23 (60.9%)	0.145
>40	44/177 (24.9%)	133/177 (75.1%)	
Gender			
Males	47 (29.2%)	114 (70.8%)	0.080
Females	6 (15.4%)	33 (84.6%)	
Medical history n (%)			
Hypertension	26/101 (25.7%)	75/101 (74.3%)	0.806
Diabetes mellitus	20/73 (27.4%)	53/73 (72.6%)	0.827
Left ventricular ejection fraction n (%)			
<40%	22/85 (25.9%)	63/85 (74.1%)	0.864
40-49%	24/83 (28.9%)	59/83 (71.1%)	0.514
>49%	7/32 (21.9%)	25/32 (78.1%)	0.517
SYNTAX score n (%)			
Low (<22)	42/92 (45.7%)	50/92 (54.3%)	**0.0001**
Intermediate (22-32)	7/71 (9.9%)	64/71 (90.1%)	**0.0001**
High (>32)	4/37 (10.8%)	33/37 (89.2%)	**0.0001**
Cholesterol >200, mg/dL	2/25 (20.0%)	20/25 (80.0%)	0.431

Triglycerides >150 mg/dL	12/48 (25.0%)	36/48 (75.0%)	0.787
High density lipoprotein <40 mg/dL	25/90 (27.8%)	65/90 (72.2%)	0.711
Low density lipoprotein >200 mg/dL	14/73 (19.2%)	59/73 (80.8%)	0.075

[Table/Fig-2]: Association between demographic variables and Lp(a). p-value of <0.05 was considered as statistically significant

DISCUSSION

The present study was conducted to evaluate Lp(a) as independent risk factor for CAD. The study revealed a correlation between Lp(a) and severity of CAD as assessed by the SYNTAX score. Patients with Lp(a) >25 mg/dL displayed greater severity of CAD as compared to patients with Lp(a) <25 mg/dL.

Kamariya CP et al., conducted a case-control study to assess the correlation between Lp(a) and young Myocardial Infarction (MI) patients [11]. Their results indicated significantly increased levels of Lp(a) in young MI patients. In contrast, the current study reports elevated Lp(a) levels (>25 mg/dL) in 60.9% patients <40 years compared to 75.1% in patients >40 years, although not statistically significant. The findings may be justified by increased levels of Lp(a) in majority of MI cases irrespective of age. Furthermore, Pare G et al., revealed high Lp(a) levels were associated with an increased risk of MI independent of established MI risk factors, including diabetes mellitus, smoking, high blood pressure, and apolipoprotein B and A ratio [12].

Literature has consistently evidenced elevated plasma concentrations of Lp(a) as a risk factor influencing the development of a variety of thrombotic and atherosclerotic disorders. Senthilkumari S and Ramadevi M, aimed to observe whether Lp(a) is significantly elevated in patients with acute coronary syndrome in comparison to healthy controls or not [13]. The study found mean plasma Lp(a) levels and lipid parameters were significantly higher in the study group (23.87±7.56 mg/dL) as compared to control group (10.4±3.11 mg/dL) (p=0.0001). In the present study, Lp(a) levels were increased in majority of CAD patients, 73.5% of the patients (147/200 cases) had high Lp(a) (>25 mg/dL) levels and only 26.5% (53/200 cases) had low levels of Lp(a) (<25 mg/dL).

Majority of the patients in the present study were males. Males contributed 80.5% of the study population whilst females contributed only 19.5%. This finding is in agreement with the study performed by Mosca L et al., which revealed higher prevalence of CAD in men [14]. Furthermore, in the present study, 70.8% of males had high Lp(a) while remaining 29.2% had low Lp(a). Amongst females, 84.6% had high Lp(a) and 15.4% had low Lp(a). However, no significant association was found between Lp(a) and gender (p-value=0.08) which is in line with study findings by Senthilkumari S et al., where there was no significant difference observed in Lp(a) level between males (24.52±7.33 mg/dL) and females (22.89±7.99 mg/dL) [13].

The SYNTAX score is an angiographic grading tool to determine complexity of CAD. Higher values are indicative of more complex disease with potentially worse prognosis [15, 16]. Habib SS et al., conclude higher Lp(a) levels are associated with more severe and diffuse blockage of the coronary vessels [17]. Lp(a) levels correlated significantly with coronary vessel score (p-value=0.033). Additionally, Gupta R et al., indicated that measurement of Lp(a) provides a better marker for predicting the presence of angiographically defined CAD as compared to traditional measures [18]. Similarly, Dahlen GH et al., found that Lp(a) levels were independently and significantly associated with presence of CAD (p-value <0.021) and tended to correlate with lesion scores [19]. Hikita H et al., reported total number of plaques, number of non calcified plaques and low attenuation plaques were significantly higher in the group Lp(a) level of ≥25 mg/dL as compared to the group with Lp(a) level of <25 mg/dL [20]. In the present study, greater percentage of patients with intermediate (90.1%) and high SYNTAX (89.2%) scores had high Lp(a) levels as compared with patients with low SYNTAX score. Lp(a) was significantly associated with SYNTAX score. Thus, Lp(a) is significantly associated with severity of CAD.

The CAD has multiple risk factors such as diabetes, hypertension, dyslipidemia, smoking and many more. Studies regarding association of the mean Lp(a) levels with diabetes are contradictory. Singla S et al., found a higher mean concentration of Lp(a) in a diabetic subjects [21]. Holanda M et al., found no difference in the mean Lp(a) concentration between diabetic and non diabetic subjects [22]. In the present study, high values of Lp(a) were found in diabetic patients (72.6%) while non diabetic patients (27.4%) had low Lp(a). However, no significant association was found between Lp(a) and diabetes mellitus in this study. Correlation between Lp(a) and hypertension was also studied in this study, 74.3% of hypertensive patients had high Lp(a) while 25.7% had low Lp(a). This finding is in concordance with a similar study conducted by Ghorbani A et al., where, no significant association was found between Lp(a) and stages of hypertension [23].

Limitation(s)

The enrolled subjects might not have been representative of the entire population with CAD, as they were referred for coronary angiography in tertiary care hospitals. Also, moribund patients, patients who cannot tolerate coronary angiography or patients not willing to consent for coronary angiography were not included in the study.

CONCLUSION(S)

High lipoprotein values were associated with high SYNTAX score and thus have poor prognosis. However, future studies are warranted to investigate potential genetic influence of Lp(a) levels and the role of screening Lp(a) levels as a method of primary prevention of CAD.

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