ASSESSMENT OF SERUM LIPOPROTEIN (a) LEVEL IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION IN DIFFERENT AGE GROUP

Nusrat Sharmin Anny[1*] Md Qamrul Islam[2] Nayeema Tasneem[3]
S M Khaled[4] Rehana Aziz[5] Mahmudul Haque[5]

Abstract

Background : Coronary Artery Disease (CAD) is one of the major causes of increased morbidity and mortality in developed and developing countries. Acute myocardial infarction is the most important consequence of coronary artery disease. Lipoprotein (a) is considered as a risk factor for acute myocardial infarction. The aim of the present study is to evaluate serum lipoprotein (a) level with acute myocardial infarction in different age group and to observe association of Lp (a) with diabetes mellitus in patients with AMI.

Matherials and methods : This was a hospital based cross-sectional study was conducted in the Department of Biochemistry & Cardiology of Chittagong Medical College Hospital from July 2018 to June 2019 with one hundred (100) patient with AMI and seventy (70) healthy people age ranging from 21 to 80 years.

Results: Serum lipoprotein (a) level were significantly higher in patients with AMI (Cases) than that in healthy subjects (Controls) (40.47 ± 2.47mg/dl vs 20.42 ± 2.47mg/dl. The mean serum Lp (a) value was found increasing with age in patients with AMI (<40 year: 36.96 ± 7.93mg/dl, 40-60 year : 41.19 ± 3mg/dl and >60 year : 41.75 ± 4.95mg/dl.

Conclusion: Serum Lp (a) level was significantly higher in patients with AMI. Serum Lp (a) level also increases with age, though the difference was not statistically significant. Estimation of serum Lp(a) level may project an early and important information for patients prior to acute MI.

Key words: Serum Lp (a); lipid profile; AMI.

1. Lecturer of Biochemistry
Chittagong Medical College, Chattogram.
2. Indoor Medical Officer of Nephrology
Chittagong Medical College Hospital, Chattogram.
3. Associate Professor of Biochemistry
Chittagong Medical College, Chattogram.
4. Laboratory Director
Epic Health Care, Chattogram.
5. Professor of Biochemistry (Retired)
Chittagong Medical College, Chattogram.

***Correspondence:** **Dr. Nusrat Sharmin Anny**
E-mail: nusratsharmin2014@gmail.com
Cell : 0171774 69 28

Submitted on : 30.10.2020
Accepted on : 17.11.2020

Introduction

Cardiovascular disease is a global public health problem. It contributes to 30% of total mortality and 10% of the global disease burden.[1] The burden of cardiovascular disease rising both in developed and developing countries.[2] Myocardial infarction is one of the five main manifestations of Coronary Heart Disease (CHD). Myocardial infarction is defined as myocardial necrosis due to loss of blood supply to an area of myocardium.[3]

The pathogenesis of Acute Myocardial Infarction (AMI) is multifactorial, impaired lipid metabolism is one of the crucial factors in development of AMI.[4] Lipoprotein (a) is a complex lipoprotein consisting of a central core of LDL, covalently linked by a disulphide bond to a apoprotein (a).[5] The Copenhagen City Heart Study (CCHS) found that extremely elevated Lp (a) levels increases the risk of myocardial infarction 3-4 fold.[6] Elevated Lp(a) level was the most common risk factor in the CADI (Coronary Artery Disease in Asian Indians) study.[7]

Lp (a) was discovered in human serum in 1963 by Kare Berg.[8] Lp (a) is a LDL like particle synthesized by the liver in which a large glycoprotein, apolipoprotein (a) is covalently bound to apo B100 by a disulfide bond.Disulfide bond exists between apo(a) cys4057 and apo B cys4326. Lp (a) plasma concentrations are highly heritable and mainly controlled by the LPA gene located on chromosome 6q26-27.[9] Apo (a) synthesized in hepatocytes and assembled with circulating LDL particle at the hepatocyte cell membrane to form lipoprotein(a). Then come to plasma. The half-life of Lp (a) in the circulation is about 3-4 days.[10]

Lp (a) has structural similarity with plasminogen and causes competitive inhibition of tissue plasminogen activator-1. This causes reduced fibrinolysis and stimulation of secretion of plasminogen activator inhibitor-1.[11] Lp (a) may also enhance coagulation by inhibiting the function of tissue factor pathway inhibitor.[12] Lp (a) also promotes platelet aggregation.[13] Lp (a) contributes to the process of

atherogenesis. Lp (a) binds to triglyceride rich lipoproteins and causes accumulation of lipid in the arterial wall. Lp (a) undergoes oxidation and taken up by macrophage, thereby forms foam cell.[13] Lp (a) also has inflammatory property that promote chemotaxis of monocytes and leads to smooth muscle cell proliferation.[14] In a recent study by Pelligrino et al has seen that the apo(a) component of Lp(a) induces rearrangement of actin fibers in cultured endothelial cells. This leads to a loss of cell to cell contact, which may contribute to the initial damage and increase endothelial layer permeability that precedes the atherosclerotic lesion.[15]

Serum Lp (a) level has been found to be associated with dyslipidemia, obesity, hypertension and diabetes mellitus.[16-18] A high serum Lp (a) level is a significant predictor of long term adverse outcome in AMI patients treated by primary percutaneous transluminal coronary angioplasty.[19] Diabetes Mellitus is a major public health problem that is approaching epidemic proportions worldwide.[20] Recent evidence suggests that Lp (a) also increases in type 2 diabetes mellitus.[21] Serum Lp (a) is now considered as a new risk factor for cardiovascular disease and showed a genetic link to accelerate atherogenesis in diabetes mellitus.[22] In a South-Asian study the prevalence rates for elevated Lp (a) in type 2 diabetes mellitus was found 43.4% and it was 26.7% in nondiabetic people.[23] Young patients with CAD are specific subset of population requiring attention.[24] The overall age standardized mortality ratio of CAD in Asian males compared to white males was 37.3% higher in age group of 20-29 years. Asian Indians belonging to different countries have the same high mortality.[25]

European Atherosclerosis Society Consensus Panel has recommended screening for Lp (a) levels, in order to identify those at intermediate or high risk of CVD.[26] Aim of this study is to evaluate value of Lp (a) for the patients with acute MI in different age group and to observe association of serum Lp (a) level with diabetes mellitus in cases.

Materials and methods

The study was a cross-sectional study, was conducted in the Department of Biochemistry, Chittagong Medical College (CMC) and indoor patients in Coronary Care Unit of Department Cardiology, Chittagong Medical College Hospital, between July 2018 to June 2019. Patients with Acute Myocardial Infarction (AMI) and healthy subjects were considered age ranging from 21-80 years were enrolled by non probability consecutive sampling technique as per fulfillment of inclusion criteria. Stroke, renal failure, liver failure, acute infection, malignant disease were excluded. Informed consent was taken from the participants. A predesigned case record form was used to record relevant clinical, medical, demographic, socio-economic data. The study was approved by the ethical review committee CMC. Serum Lp (a) were measured by nephalometry in Siemens BN proSpec analyzer. History of diabetes mellitus was included as another variable. Microsoft Excel and IBM-SPSS v. 20 for windows were used for data processing and analysis. Statistical inference was based on 95% confidence interval p value <0.05 was considered statistically significant. Variables were expressed as mean ± Standard Errors of Mean (SEM). Student 't' test and chi ($\chi^{2)}$ square test were used to see associations.

Myocardial infarction[27]: Myocardial Infarction (MI) may be defined by the demonstration of myocardial cell necrosis due to significant and sustained ischaemia. The WHO European myocardial infarction registry criteria were based on clinical history findings on the Electrocardiogram (ECG) and enzyme measurements in blood. MI was diagnosed in the presence of one of the following:

i) ECG showing unequivocal pathological Q waves and/or ST segment elevation or depression in serial recordings.

ii) History of typical or atypical angina pectoris, together with equivocal changes in the ECG and elevated enzymes.

Desirable level of Lp (a) :[9]

Normal : <14 mg/dl (< 35 nmol/L),
Borderline risk : 14 - 30 mg/dl (35 - 75 nmol/L)
High risk : >30 - 50 mg/dl (75 - 125 nmol/L)
Very high risk : >50 mg/dl (>125 nmol/L)

Diabetes Mellitus:[28] Fasting plasma glucose ≥ 7 mmol/L, 2-hours after 75gm glucose > 11.1 mmol/L. Type 2 diabetes mellitus is characterized by hyperglycemia, insulin resistance and relative insulin deficiency.

Results

A total number of 170 subjects age ranging from 21 to 80 years were included as per fulfillment of inclusion and exclusion criteria. 100 subjects were patients with AMI named group A and 70 healthy subjects were termed as group B.

Table I : Distribution of serum lipoprotein(a)among the study groups (n = 170).

	Study Groups	n	Mean	± SEM	Range	t-test* Significance
Serum	Group A	100	40.47	2.47	9.94 – 95.00	p < 0.001
Lipoprotein (a)	Group B	70	20.42	2.47	8.00 – 80.00	Highly
(mg/dl)	TOTAL	170	33.79	1.99	8.00 – 95.00	Significant

This table demonstrates mean values of Lp (a) in group A and group B were 40.47mg/dl ± 2.47 SEM and 20.42mg/dl ± 2.47 SEM respectively. Significant difference (p<0.001) was found in mean values between two groups (Table I).

Table II : Association between serum lipoprotein (a) status and the study groups.

Serum Lipoprotein(a) Status	Study Groups (n = 100) Group A	(n = 70) Group B	Total (n = 170)	Chi-square test significance
Normal	18 (18.0)	45 (64.28)	64 (37.64)	p < 0.001 Highly
Borderline Group	22 (22.0)	14 (20.0)	36 (21.18)	Significant
High Risk Group	60 (60.0)	10 (14.28)	70 (41.18)	

● Figures within parentheses indicate percentages

There was a highly significant (p<0.001) association of serum lipoprotein (a) status among group A and group B (Table II).

Table III : Distribution of serum lipoprotein (a) within the different age groups among the cases (n=100).

	Age in Groups	n	Mean	± SEM	Range	ANOVA test Significance
Serum	< 40 Years	14	36.96	7.93	9.94 – 95.00	p > 0.05
Lipoprotein(a)	40 – 60 Years	57	41.19	3.00	9.94 – 95.00	Not
(mg/dl)	> 60 Years	29	41.75	4.95	9.94 – 87.30	Significant

This table demonstrates mean values <40 years age 36.96mg/dl ± 7.93 SEM, 40-60 years age 41.19mg/dl ± 3 SEM, >60 years age 41.75mg/dl ± 4.95 SEM. The association was not significant (p>0.05) (Table III).

Table IV : Association between serum lipoprotein (a) status and the age groups among the cases (n=100).

Serum Lipoprotein (a) Status	Age in Groups < 40 Years	40-60 Years	> 60 Years	Total	Chi-square test significance
Normal	6 (42.9)	8 (14.0)	5 (17.2)	19 (19.0)	p > 0.05
Borderline Group	1 (7.1)	14 (24.6)	7 (24.1)	22 (22.0)	Not
High Risk Group	7 (50.0)	35 (61.4)	17 (58.7)	59 (59.0)	Significant
Total	14	57	29	100 (100.0)	

In this study serum Lp (a) value was found to be changed with age. This table shows the changes, though it was not significant, the mean values of Lp (a) were seen increased with age in patients with AMI (Table IV).

Table V : Distribution of serum lipoprotein(a) according to diabetic status among the cases (n = 100).

	Diabetes	n	Mean	± SEM	Range	t-test* Significance
Serum	Present	30	44.50	4.88	9.94 – 95.00	p > 0.05
Lipoprotein (a)	Absent	70	38.75	2.83	9.94 – 95.00	Not
(mg/dl)	TOTAL	100	40.47	2.47	9.94 – 95.00	Significant

This table shows the mean values of Lp (a) were 44.50mg/dl ± 4.88 SEM and 38.75mg/dl ± 2.83 SEM in diabetic and non diabetic patients respectively. Association between the means was not statistically significant (p>0.05) (Table V).

Table VI : Association between serum lipoprotein(a) status and diabetes among the cases (n = 100).

Serum Lipoprotein (a) Status	Diabetes Present (n = 30)	Absent (n = 70)	Total (n = 100)	chi-square test significance
Normal	4 (13.3)	15 (21.4)	19 (19.0)	p > 0.05
Borderline Group	7 (23.3)	15 (21.4)	22 (22.0)	Not
High Risk Group	19 (63.4)	40 (57.2)	59 (59.0)	Significant

● Figures within parentheses indicate percentages

In this study serum Lp (a) status in diabetic patients was not significantly associated (p>0.05) with that of non diabetic patients with AMI. This table presents that 13.3% diabetic patients with AMI had Lp (a) within normal limit, 23.3% had within borderline and 63.4% had in high risk group (Table VI).

Discussion

This study shows comparison of serum Lp (a) concentration in patients with acute myocardial infarction of different ages and healthy normal

subjects. This study has shown that serum Lp (a) level was significantly higher ($p<0.001$) in patients with AMI than that in healthy subjects in t-test (Table-I). In this study sixty percent (60%) AMI patients had high serum Lp (a) concentration, while only fourteen percent (14.28%) healthy subjects had high serum Lp (a) concentration. Sixty four percent (64.28%) healthy subjects had desirable serum Lp (a) concentration and in case of AMI patients that was only eighteen percent (18%) (Table-II). There are some studies where serum Lp (a) concentration were found increased in patients with AMI. Biswajit Majumder et al showed that there was a significant ($p<0.05$) difference in Lp (a) concentrations between patients with AMI and healthy subjects.[29] In a study done by Debnath T, it was shown that the mean serum Lp (a) concentration was significantly higher ($p<0.005$) in AMI patients than that in control group.[30] Kamariya et al also found that the difference in Lp (a) levels between the patients of AMI and control group was highly significant ($p <0.001$) suggesting Lp (a) as an important predictor of coronary heart disease.[25] HK Tamang et al. showed significantly high ($p<0.005$) serum Lp (a) levels in cases of AMI patients than controls.[31] Serum Lp (a) were found to be increased with age in patients with AMI in anova test (Table-III). A study showed that the plasma Lp (a) level increases with age both in patients and controls.[32] Moreover most of the AMI patients (61.4%) age between 40-60 years were in high risk group of Lp (a) (Table-IV). The maximum value of serum Lp (a) levels were seen in 51-60 years age group in a study done by Akila and Prabhakar.[22] In this study there was no significant ($p>0.05$) difference in mean serum Lp (a) values among diabetic and non diabetic patients with AMI in t-test (Table-V). Association between serum Lp (a) and diabetes mellitus in patients with AMI was also not statistically significant ($p>0.05$) in chi-square test (Table-VI). Few other studies also suggested that there were no significant association of increased serum Lp(a) status with diabetes mellitus.[33,34] Nabil Bashir et al. demonstrated that the effect of diabetes and smoking risk factors increased plasma level of Lp (a) in males >50 years old.[32] In another study it was shown that type-2 DM patients with AMI had significantly higher ($p<0.001$) Lp (a) level compared to non-diabetic AMI patients.[22] Ashfaq et al also showed that the level of Lp (a) was significantly higher ($p<0.001$) in diabetic than non-diabetic AMI patients.[35]

Limitations

There are certain limitations in this study:

- Sample size in this study was small
- Cross sectional study is a weak study to establish associations
- The study was conducted in a single hospital
- The anthropometric measurements were done once.

Conclusion

In this study serum Lp (a) levels were significantly higher in patients with AMI. Mean Lp (a) level were increased with advanced age So the assessment of serum Lp (a) level as a routine test may provide a baseline information regarding Lp (a) level in AMI patients.

Recommendations

- Study should be done with large sample size in different hospitals
- Cohort study should be done for more practical information
- Lipoprotein (a) related attention should be raised and its determination should make a routine test to minimize the lipid related complications.

Acknowledgement

We are very grateful to the patients who participated in the study with immense patience. We are also thankful to all the doctors and stuffs of the Department of Biochemistry, CMC and Department of Cardiology, CMCH. We are thankful to Mr. Sanowar who helped in laboratory procedures. This work would not be possible without their cooperation.

Contribution of authors

NSA-Conception, design, acquisition of data, drafting & final approval.
MQI-Data analysis, drafting & final approval.
NT-Acquisition of data, critical revision & final approval.
SMK-Data analysis, critical revision & final approval.
RA-Interpretation of data, critical revision & final approval.
MH-Design, critical revision & final approval.

Disclosure

All the authors declared no competing interests.

References

1. World Health Organization. World Health Statistics 2008. Geneva: WHO. 2008.

2. Yusuf S, Hawken S, Ounpuu S et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (The INTERHEART study): Case-control study. Lancet. 2004;364:937–952.

3. Jo Anne Micaly Foody: Cardiovascular risk factors: Manual of Cardiovascular Medicine, 2nd Ed. Brian. P. Griffin, Eric J. Topol. (Eds.), Lippincott Williams and Wilkins, Philadelphia. 2004.

4. Khan HA, Alhomida AS, Sobki SH. Lipid profile of patients with acute myocardial infarction and its correlation with systemic inflammation. Biomark Insights. 2013; 8: 1-7.

5. Rajini P. V, Kashi Babu A. Evaluation of lipoprotein (a) levels in young patients with myocardial infarction in north costal Andhra region. Journal of Evolution of Medical and Dental Sciences. 2015;4(5):808-814.
DOI: 10.14260/jemds/2015/116.

6. P. R. Kamstrup, M. Benn, A. Tybjaeg-Hansen, and B. G. Nordestgaard, Extreme lipoprotein (a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study, • Circulation. 2008;17(2):176-184.

7. Gambhir JK, Kaur H, Gambhir DS, Prabhu KM. Lipoprotein (a) as an independent risk factor for coronary artery disease in patients below 40 years of age. Indian Heart J. 2000;52:411-415.(s)

8. Berg K. "A New Serum Type System In Man--The LP System". Acta Pathol Microbiol Scand. 1963;59 (3): 369–382.
doi:10.1111/j.1699-0463.1963.tb01808.x. PMID 14064818.

9. Lipiprotein (a) Wikipedia- Structure and reference value of Lp (a).

10. Erqou S, Kaptose S, Perry PL, Di Angelantonio E, Thompson A, White IR et al. Apolipoprotein (a) isoforms and the risk of vascular disease: Systematic review of 40 studies involving 58,000 participants. J Am Coll Cardiol. 2010;55(19):2160-2167.

11. Banach M, Aronow WS, Serban C, Sahabkar A, Rysz J, Voroneanu L, Covic A. "Lipids, blood pressure and kidney update 2014". Pharmacological Research. 2015;95-96: 111–125.
doi:10.1016/j.phrs.2015.03.009. PMID 25819754.

12. Pan S, Kleppe LS, Witt TA, Mueske CS, Simari RD. "The effect of vascular smooth muscle cell-targeted expression of tissue factor pathway inhibitor in a murine model of arterial thrombosis". Thrombosis and Haemostasis. 2004;92 (3): 495–502.
doi:10.1160/TH04-01-0006. PMID 15351845.

13. McCormick S P.A. Lipoprotein (a) : Biology and Clinical importence. University of Otago, New Zealand. Clin Biochem Rev. 2004;25.

14. Journal of the American Heart Association. "Lipoprotein (a)-We Know So Much Yet Still Have Much to Learn …". Banach M. 2016;5 (4): e003597.
doi:10.1161/JAHA.116.003597. PMC 4859302. PMID 27108250.

15. Pellegrino M, Furmaniak-Kazmierczak E, LeBlanc JC et al. The apolipoprotein (a) component of lipoprotein (a) stimulates actin stress fiber formation and loss of cell-cell contact in cultured endothelial cells. J Biol Chem. 2004.

16. Wang J, Zhang C, Chen D, Liu X, Feng X. Lipoprotein (a) and its immune complexes in dyslipidemic subjects. Clin Biochem. 2004;37:710–713.

17. Holanda MM, Filizola RG, Costa MJ, Andrade RV, Silva JA.Plasma lipoprotein (a) levels: A comparison between diabetic and non-diabetic patients with acute ischemic stroke. Arq Neuropsiquiatr 2004;62:233-236.

18. Sinha R, Bhushan I. Study of serum lipoprotein (a) and lipid profile in patients with untreated essential hypertension in north indian population. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS). 2015;14(9):VI:47-50.

19. M Michele, V Marco, R Cristina. Lipoprotein (a) in Cardiovascular disease. Biomed Res Int. 2013, ID 650989.
DOI: 10.1155/2013/650989.

20. Diabetes Atlas. Eight Edition. International Diabetes Federation. 2017.

21. Peela J R, Latiwesh O B, Elshaari F et al. Investigating the Atherogenic Risk of Lipoprotein (a) in Type 2 Diabetic Patients. Cureus. 2018; 10(7): e3030.
DOI 10.7759/cureus.3030.

22. Akila S, Prabhakar. Comparative study of Lipoprotein (a) in type 2 diabetics and nondiabetics with acute coronary syndrome. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS). 2016;15(8)VII:55-60.
DOI: 10.9790/0853-1508075560.

23. Habib SS, Aslam M. High risk levels of lipoprotein (a) in Pakistani patients with type 2 diabetes mellitus. Saudi Med J. 2003; 24 (6): 647-651.

24. Akram V M, Zaidi F, Bansal F. A study of risk factors in young patients of myocardial infarction. Int J Res Med Sci. 2015;3(10):2677-2681.
doi.org/10.18303/2320-6012.ijrms20150813.

25. Kamariya C P, Gorasia J H, Vachhani U. Evaluation of serum lipoprotein (a) in young patients with myocardial infarction. Int J Med Public Health. 2014;4:107-109.
DOI:10.4103/2230-8598. 127169.

26. Davidson MH, Ballantyne CM, Jacobson TA. Clinical utility of inflammatory markers and advanced lipoprotein testing: Advice from an expert panel of lipid specialists. J Clin Lipidol. 2011; 5: 338-367.

27. Mendis S, Thygesen K, Kuulasmaa K, Giampaoli S. World health organization definition of myocardial infarction: 2008-09 revision. Int. J. Epid. 2011; 40: 139-146.

28. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2018;41(Suppl-1): S13-S27.
doi: 10.2337/dc18-S002.

29. Albers JJ, Koschinsky ML, Marcovina SM. Evidence mounts for a role of the kidney in lipoprotein (a) catabolism. Kidney Int. 2007;71(10):961-962.
doi:10.1038/sj.ki.5002240.

30. Debnath T, Roy S, Mondal M C. Assessment of lipoprotein (a) in acute myocardial infarction patients: As risk factor. 2016;6(4).
ISSN-2249-555X,IF:3919,IC Val:74.50.

31. Tamang HK, Timilsina U, Singh R. Serum lipoprotein(a) concentration is a better predictor of myocardial infarction than traditional lipopd profile and lipid ratios. Int. J App Sci Biotechnol. 2017;1(3):106-109.
Doi: 10.3126/ijasbt.vli3.8583.

32. Saleh A, Bashir N, Awwaa I A; Lipoprotein (a) and apolipoprotein (a) isoforms in patients with acute myocardial infarction. Am. Med. J. 2010;1(1):71-76.

33. Peng Y, Shao Z, Jiang J. Association between serum Lp (a) levels and major adverse cardiovascular events in chinese patients with ST segment elevation myocardial infarction. Int, J Clin Exp med. 2017;10(1): 897-904.

34. Afshar M, Pilote L, Dufresne L; Lipoprotein(a) interactions with LDL-cholesterol and other cardiovascular risk factors in premature ACS. J Am Heart Assoc. 2016;5: e003012.
doi: 10.1161/JAHA.115003012.

35. Ashfaq F, Goeel P K, Khan M I, Ali W; Lipoprotein (a) levels in relation to severity of coronary artery disease in north Indian patients. 2018; IP:103.73.105.243.
doi: 10.4103/1995-705X.107114.