

Relationship between Lipoprotein (a) and Acute Myocardial Infarction**Dr. M. Saradha¹, Dr. Saravanan B²**¹Professor and Head, Department of Biochemistry, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India²Assistant Professor, Department of Biochemistry, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India**Original Research Article*****Corresponding author***Dr. Saravanan B***Article History***Received: 01.09.2018**Accepted: 05.09.2018**Published: 30.09.2018***DOI:**

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Abstract: Acute Myocardial Infarction (AMI) is one of the most common causes of mortality in human beings. To the multifactorial risk factors of AMI, a small lipoprotein, Lp(a) has been included as an independent risk factor for premature atherosclerosis and AMI because of the prothrombotic and proatherogenic properties of the Lp(a). With the above view, this study aimed to find the association between Lp(a) and AMI, the diagnostic efficacy of Lp(a) in the confirmation of AMI and if the intensity of Lp(a) increase is related to the development of Atherosclerosis, the prime causative factor of the former disease. The biochemical determination of Lp(a) along with serum analysis of CPK-MB, Lipid profile, Blood Urea and sugar were undertaken altogether in 80 subjects of whom 40 were apparently normal subjects. 40 AMI patients without history of smoking, wherein AMI is proved by coronary angiography and who came 4-6 weeks after the attack for review to Cardiology OP has been selected for study population. There is no appreciable change in the level of any of the parameters with respect to sex. There is a highly significant increase in Serum Lp(a) level, Serum TGL, Total Cholesterol and LDL-C levels in AMI patients when compared to the controls. There is a positive correlation of Lp(a) with lipid fractions – TC, LDL-C, TGL. By analysing the sensitivity, specificity, positive predictive value and negative predictive value for various cut off values, 28 mg% was selected as the most approximate cut off level of Lp(a). Above 28 mg%, Lp(a) can speed up atherosclerosis resulting in AMI. Increase in Lp(a) is associated with AMI and the increase is due to inheritance of higher Lp(a) levels which should have existed even before the occurrence of the disease.

Keywords: Acute Myocardial Infarction (AMI), Lipoprotein (a), Atherosclerosis, Ischemic Heart Disease (IHD), Lipid profile.

INTRODUCTION

Ischemic Heart Disease (IHD) today has been pronounced as the leading cause of death by WHO as it is the scourge of modern civilisation. The disease is generally understood to be a malady of the middle and old ages although Atherosclerosis (AS), the underlying lesion of IHD begins in childhood. AMI (Acute Myocardial Infarction) is one among the IHD which is the most common cause of mortality in human beings. The mortality due to AMI has been steadily increasing in spite of advancement in Medicine due to the stress and strain of modern world. It is at present said to be approximately 30%, with more than half of the deaths due to the disease occurring before the stricken individual reaches the hospital.

AMI, which is due to myocardial damage, generally occurs when there is an abrupt decrease in coronary blood flow following a thrombotic occlusion of coronary artery previously narrowed by Atherosclerosis. Infarction has also been found to occur when a coronary artery thrombus develops rapidly at the site of a vascular

injury, which injury may be facilitated by factors like Cigarette smoking, Hypertension and lipid accumulation. In rare cases, infarction may also be due to coronary artery occlusion caused by coronary emboli occurring as a result of dislodged thrombus from elsewhere, Congenital abnormalities, Coronary spasm and a wide variety of systemic diseases. The intensity of myocardial damage that is produced as a result of coronary occlusion due to various causes enumerated, depends on the territory supplied by the affected vessel, degree of occlusion, native factors that produce early spontaneous lysis of the occlusive thrombus, the presence of collaterals, the quantity of blood supplied by the collateral vessels to the damaged area and the demand for O₂ by the affected myocardium. The multifactorial etiological factors of the disease was so long said to include Cigarette smoking, Obesity, Hypercholesterolaemia, Hypertension, Diabetes mellitus and Family History of IHD along with the stress and strain of the modern world. To the above risk factors of IHD, a small lipoprotein, Lp(a) has been included and

much work on the lipoprotein are in progress to study its role in IHD[1].

Lp(a) is said to be expressed in the First year of life and is found to be a variant of LDL. Shortly it became apparent that Lp(a) by itself is a distinct particle rather than an allelic variant of LDL[2-5]. Lp(a) is a complex assembled from two very different components which form the central and the outer core [2, 4, 6]. The central core which is hydrophobic is formed by LDL. The lipid fraction of LDL is constituted by all lipids and its protein fraction by Apo B-100. The outer core of Lp(a) is found to be Apo(a) which is a hydrophilic glycoprotein with a uniquely high degree of conserved internal repeat structure and an enormous size heterogeneity[4,6]. Hence while LDL contains only Apo B-100, Lp(a) contains both Apo B-100 and Apo (a)[7].

Apo (a) is composed of a kringle containing domain and a serine protease domain [8-12]. "Kringles" which are sequences of 80-90 amino acids are internally stabilised by 3 cross linking disulphide bridges [2, 4]. The Kringle structure has been discovered not only in Apo (a), but also in certain other protein molecules namely Plasminogen, tPA, Urokinase, Prothrombin, Protein -C, Coagulation factors VII, IX, X, XIII.[2,4] Though the Kringles in the above enumerated proteins are of 5 types, referred to by Roman numerals I-V, Apo (a) contains only 2 types of Kringles namely type IV & V [2, 3, 4].

Though the extensive homology of Apo (a) with Plasminogen has raised the possibility that Apo (a) may function similar to the former protein in the fibrinolytic process, it has been found that it is not so. In fact, the reality is that Apo (a) interferes with many steps in the complex biochemical cascades of reactions involved in Plasminogen mediated Fibrinolysis [13]. Lp(a) is also found to aid in the formation of fibrin network where the proteins Fibrin, Fibronectin, Fibrinogen and Apo (a) are held as a mesh by cross linking between Endo- γ -glutamyl and Endo- ϵ -lysyl residues of the above proteins [4]. The cross linking of the above (protein) surface structures aids in the deposition of Lp(a) in the growing atherosclerotic plaques. Lp(a) forms complexes with proteoglycans and are taken up by macrophages [14]. Lp(a) which is converted to oxidised Lp(a) by polymorphonuclear leucocytes are also-taken up by macrophages via Scavenger Receptors. Both lead to foam cell formation and cytokine production which act as chemo attractants and mitogens for smooth muscle cells. Plasmin is said to activate Transforming Growth factor - β (TGF- β) and thus contribute to blocking of smooth muscle cell proliferation. Lp(a) by down regulating plasmin generation, leads to impaired activation of TGF- β and contribute to smooth muscle cell proliferation [3, 4, 14]. Lp(a) is also said to decrease production of endothelium derived growth factor (EDGF) and increased production

of adhesive glycoprotein – Intercellular adhesion molecule – 1 (ICAM- 1)[3, 4].

The prothrombotic and proatherogenic properties attributed to the lipoprotein are a consequence of the above, which aid the formation of Atherosclerotic plaques. Hence Lp(a) is considered to be an independent risk factor for premature atherosclerosis and IHD. The informations so far gathered about the lipoprotein Lp(a), gave the impetus to biochemically estimate serum Lp(a) in health and in those diseases where it is considered to be a risk factor, so as to analyse the usefulness of its determination in the interpretation of the above disease. With the above view, this study aimed to find the association between Lp(a) and AMI, the diagnostic efficacy of Lp(a) in the confirmation of AMI and if the intensity of Lp(a) increase is related to the development of Atherosclerosis, the prime causative factor of the former disease.

MATERIALS AND METHODS

The biochemical determination of Lp(a) along with other biochemical parameters in blood was undertaken altogether in 80 subjects of whom 40 were apparently normal subjects. The 40 apparently normal subjects were from the staff of the Government Hospital and their relatives of age group 20-60 years with the 2 sexes equal in number. 40 were proven AMI patients wherein AMI is proved by coronary angiography and who came 4-6 weeks after the attack for review to Cardiology OP, Government Hospital, in Tamilnadu. Of them, those with history of smoking has been excluded from the study. 7 ml of Blood was drawn from all the above subjects from the anterior cubital vein and serum was separated from it, 1 ml of clear cell free serum was taken and preserved under - 20° C up to 4 weeks for Lp(a) estimation. Serum Lipoprotein (a) was measured by Elisa method by using Innostest Elisa kit [15]. From the remaining serum, analysis of CPK-MB, Lipid profile, Blood Urea and sugar were performed on the same day. Calculation of LDL -C and VLDL -C are done using the Formula by Friedewald. VLDL = TGL/5 and LDL-C = TC-HDL-VLDL.

RESULTS & DISCUSSION

The mean and standard deviation of Lp(a) and other biochemical parameters namely Triglycerides, Total cholesterol, HDL, LDL-C, CPK- MB, Blood sugar, Urea & Creatinine in the blood of all the 80 subjects selected for the study were tabled depending on the group to which they belong..

The mean and S.D of the parameters in males and females when compared revealed that there was no appreciable change in the level of any of the parameters with respect to sex. Hence the common mean for all the biochemical parameters irrespective of sex was selected as the controls for the study.

To find out how for Lp(a) and the other Biochemical parameters varied from controls in the diseases studied, the mean and SD of each parameter in AMI were compared with that of controls in Table 1. The statistical significance of the parameters in the

comparison Table 1 was obtained from the p value which in turn was calculated by using the students't' test. There is a highly significant increase in Serum Lp(a) level, Serum TGL, Total Cholesterol and LDL-C levels in AMI patients when compared to the controls.

Table-1: Comparison of Lp(a) and other Biochemical Parameters in Controls and in AMI Patients

PARAMETERS	CONTROL (n = 40) 20 Male; 20Female Mean±SD	AMI (n = 40) 32 Male; 8 Female Mean±SD	p Value	significance
Age	44.7±6.8	46.6±5.3	0.173	NS
Serum Lp(a) mg%	18.3±7.7	56.6±23.7	<0.001	HS
Serum TGL mg%	131.4±19.8	156.3±21.4	<0.001	HS
Serum TC mg%	175.3±15.5	211.7±36.1	<0.001	HS
Serum HDL mg%	34.2±4.4	32.3±4.7	0.069	NS
Serum LDL mg%	113.8±14.6	148.3±35.9	<0.001	HS
Serum VLDL mg%	26.3±3.9	31.3±4.2	<0.001	HS
Serum CK-MB mg%	3.8±2.2	4.2±2.1	0.358	NS
Blood sugar mg%	95.7±6.1	86.6±18.2	0.004	S
Blood Urea mg%	19.1±1.4	21.5±4.4	0.002	S
Serum Creatinine mg%	0.9±0.1	0.9±0.1	0.287	NS

Note: HS- Highly significant; S – Significant; NS – Not significant

Table-2: Pearson’s Correlation Coefficient in AMI

	r Value	p Value	Significance
Lp(a) & T.Chol	0.445	.004	S
Lp (a) & HDL	-0.339	.033	S
Lp(a) & LDL-C	0.451	.004	S
Lp(a) & VLDL	0.348	.028	S
Lp(a) & TGL	0.348	.028	S

Note: HS- Highly significant; S – Significant; NS – Not significant

Table-3: Cut off values of Lp(a) in AMI

Cut off Value of Lp(a) mg%	Sensitivity %	Specificity %	PPV %	NPV %
20	100	70	76.9	100
25	100	70	76.9	100
28	100	80	83.3	100
30	95	90	90	94.7
35	80	100	100	83.3
40	60	100	100	71.4

Note: PPV – Positive Predictive Value; NPV – Negative Predictive Value

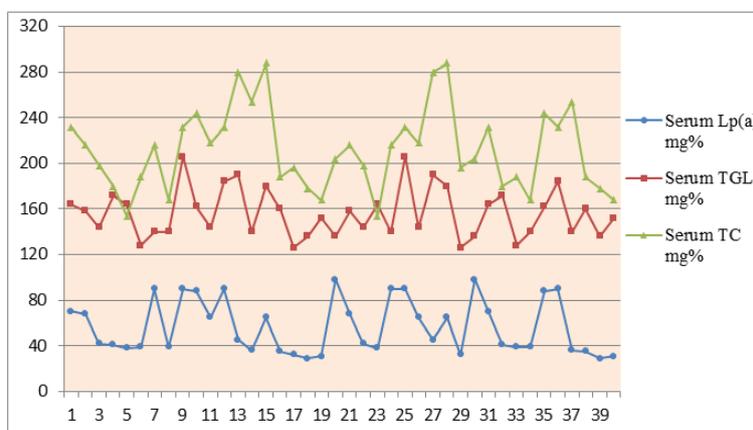


Fig-1: Line Graph showing the levels of Serum Lp(a), TC and TGL in AMI patients

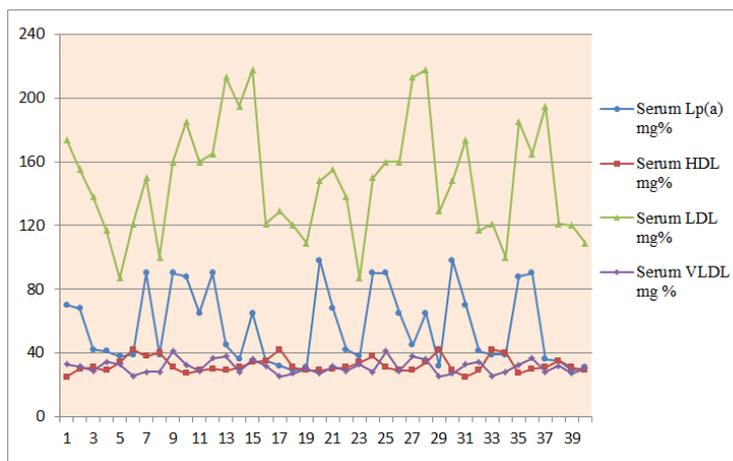


Fig-2: Line Graph showing the levels of Serum Lp(a) and Lipid parameters in AMI patients

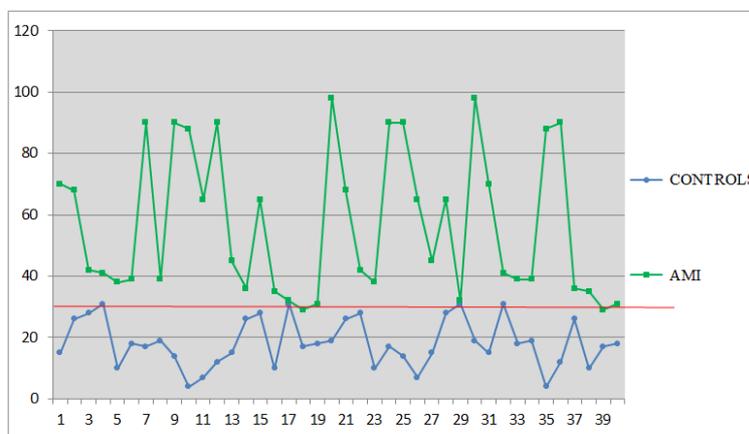


Fig-3: Line Graph showing Serum Lp(a) mg% in Controls and AMI

The mean level of 18.3 ± 7.9 mg% for Lp(a) is found to fall well within the reference range quoted by Jacques Genest Jr. *et al* which is from undetectable levels to 30 mg% [16]. The mean level of 18.3 mg% also correlates well to the level of Berg *et al* who has stated a level of 15-20 mg% as the reference range for Asian Indians. It should be remembered at this juncture that the reference range of Lp(a) in the blood is constant at any stage of life, whether it be in the new-born or adult or old age, for it has been reviewed that normally the level of Lp(a) present at the time of birth is maintained throughout the life of a subject [17]. Moreover it has been stated the plasma Lp(a) concentrations are heritable and there is striking difference in its normal concentration among various populations [16]. Eventhough the mean level of Lp(a) obtained in the study correlates to that of Jacques Genest Jr. *et al*, it is much higher to that quoted by James A. Hearn *et al* who has quoted a level of <4 mg% [18]. But the above data does not surprise the author, for James A Hearn *et al* have quoted the level for American populations unlike Jacques Genest Jr. *et al* who has quoted the same for Asian Indians. Hence the RR of Lp(a) obtained in the study from the work conducted on controls hailing from

South India should have basically inherited a high level of Lp(a) from the time to birth itself, which is found to correlate to that of Jacques Genest Jr. *et al*.

The mean level obtained for the other routine bio-chemical parameters in controls correlate well to that quoted in standard text books and of course, with the reference range of the kits where kit methodologies had been selected for evaluating their concentrations. Therefore, the mean levels obtained in the study for the various parameters in controls are found acceptable.

Scrutiny of the Table .1 where the mean levels of the parameters in AMI are compared with the mean level of controls reveal a highly significant increase (p value <0.001) for Serum Lp(a), TGL, TC and LDL-C along with a significant (p value <0.05) increase in and decrease of Blood urea and sugar respectively. Among the above, the significant increase and decrease of Blood urea and Sugar can be ignored because their mean levels in AMI are still within the reference range quoted in standard text books.

The mean level of Lp(a) (56.5 mg%) showing a highly significant increase, correlate well to the fact reviewed in literature that Lp(a) is increased in AMI and that pathological effects are noticed only above 30 mg% [19]. As Lp(a) is said to be an acute phase reactant, it is natural for Lp(a) to increase during the acute phase of M.I [19]. It is essential to remember at this stage that Acute Phase Reactant (APR) are synthesised mostly in the Liver, reach their maximum concentrations within 2-5 days of inflammation and thereafter gradually fall till they reach their original reference ranges. Even though it is a well-known fact that the time involved in the rise & fall of APR may vary, the above period is approximately 2 weeks maximum which fact has been made evident from the rise and fall of C - reactive protein (CRP), which reactant is the earliest to rise with the magnitude of increase much higher to any other APR. As the study on AMI patients was conducted only after 6 weeks from the onset of Infarct, it clearly indicates that by that time, the increase of any APR resulting as a consequence to the acute phase of infarction would have definitely subsided. Therefore, the high Lp(a) observed in the above AMI patients can be dogmatically said as being due to the already existing high blood levels of Lp(a) of the above subjects. The proof that the blood was not drawn from the AMI patients during the acute phase of the Infarction is also obtained from Serum CK-MB, which enzyme unlike its HS increase during the acute phase of MI due to its increase 4-8 hours after the Infarction with the peak level being reached in 15-24 hrs. maintains a level well within its reference range, with absence of any statistically significant increase. Hence it is ascertained that the above AMI patients have had a higher Lp(a) levels to that of controls at the time of Infarction.

It is important at this stage to emphasise that Lp(a) has been incorporated as an individual risk factor by Berg, Angelo *et al.* [19] Whether in the above AMI patients, high Lp(a) was the individual risk factor causing the infarct or whether it was a summation of effect of several risk factors like cigarette smoking, obesity, hypertension, hypercholesterolaemia, family H/O, diabetes stress and strain etc [20-22] has to be looked into. Among the various risk factors quoted cigarette smoking was excluded in the selected AMI patients and the involved biochemical parameters which have been evaluated are analysed forthwith.

Biochemical examination of blood sugar whose mean level of 86.6 ± 18.457 mg% of course has eliminated diabetes since a fasting blood sugar of 126 mg% or more than that only is diagnostic of Diabetes according to WHO norms. On the other hand, the AMI patients are found to have Hyper Cholesterolaemia and Hyper Triglyceridaemia which is evident statistically from the HS increase. The above factors are considered risk factors of AMI because Hypercholesterolaemia is said to promote atherosclerosis in coronary arteries which is the main causative factor of AMI. Moreover it

should also be noted that there is a highly significant increase of Serum LDL-C and absence of any lowering of Serum HDL-C which are the two main fractions of Serum TC promoting or preventing atherosclerosis as explained below. The increase of LDL-C is rather an important factor to be noted as it is the above cholesterol which gets deposited at the atherosclerosis site. But at the same time it should be noted that though the level of Serum LDL-C has shown a highly significant increase when compared to controls, it is still within the reference range quoted in Standard text books.

The absence of any statistical lowering of Serum HDL-C is also an important finding because HDL-C is considered as the main scavenger of tissue cholesterol as it carries cholesterol to the Liver for further metabolism or excretion and hence is able to prevent cholesterol from getting deposited at the atherosclerosis site. The above findings of Serum HDL-C and LDL-C prove that though HDL-C could not have aided the pathology of coronary atherosclerosis since it has not decreased, LDL-C should have aided the above pathology as it shows a highly significant increase.

The highly significant increase of Serum TGL in the study is acceptable. This is so because it has been reviewed that in atherogenesis, chylomicron remnants and IDL, lipoproteins derived from chylomicrons and VLDL respectively are increased. As TGL is the main lipid fraction of the above lipoproteins, it is natural to an increase in the parameters in MI which clinical condition is caused mainly by coronary atherosclerosis.

Though in the AMI group of patients, there is a highly significant increase (p value < 0.001) in the biochemical parameters suggested to promote atherosclerosis namely Serum TC and TGL, the mean level of 211.7 ± 36.662 mg% for Serum TC is just above the upper limit of its reference range and the mean level of 156.3 ± 21.77 mg% for TGL is within its reference range quoted in standard text books. Hence the statistical increase in the level of the above parameters noted in the AMI patient's perse could not have caused coronary atherosclerosis.

It is at this juncture that the increase in Lp(a) gains importance, for it has been said that Lp(a) delivers cholesterol to the atherosclerosis site. Hence, with increased Lp(a) more cholesterol can get deposited in coronary arteries leading to coronary atherosclerosis & MI. Hence, it can be inferred that high levels of Lp(a), and additional risk factor in the AMI patients could have propagated coronary atherosclerosis much more than the increase of Serum TC, by way of LDL-C or TGL could have caused.

Moreover, it should be noted that in AMI increase in Lp(a)'s mean levels from controls is ~ 3 times whereas for TC, LDL-C & TGL the degree of

increase is not even half that of Lp(a). This fact makes obvious the more dominant role of Lp(a) in the causation of AMI than the other lipid fractions. Pearson's Correlation Coefficient calculated between Lp(a) and the other lipid fractions shown in Table 2 reveal that there is a positive correlation of Lp(a) with lipid fractions – TC, LDL-C, TGL. The positive correlation of the lipid fractions in AMI is also illustrated in Figure 1&2.

Several references are available regarding the level of Lp(a) over which Coronary Artery Disease (CAD) can occur while the level quoted by James A. Hearn is 14 mg%, Berg, Kosten, Sainani & Bernaud Cantin have stated the levels to be 25, 30, 32-34 mg% respectively [23,24,25]. Hence a similar attempt is made in the study to demarcate the cutoff level of Lp(a) over which level AMI can occur. For the above purpose, Line Graphs indicating the level of Lp(a) in AMI patients and controls were drawn. Various cut off levels were selected and the sensitivity, specificity, positive predictive value and negative predictive value for them were worked out. The same are shown in Table 3. It is made clear from the above table that the most approximate cut off level is 28 mg%. The above cut off level of 28 mg% is also shown in Figure 3.

From the explanations given so far for the statistical results obtained in the table, it is clear that the high levels of Lp(a) found 6 weeks after the occurrence of the Infarct is not a sequence of the disease, but a cause of it and the above high level would have existed ever prior to the infarct as it is purely inherited. Due to the atherogenic properties of Lp(a), the subjects with the high level of the above lipoprotein are prone to the development of AMI much more than others whose level was within reference range. It is also clear that the high Lp(a) can produce AMI even in the presence of minimal hyperlipidaemia. As a cut off level of 28 mg% has been arrived at for Lp(a) in AMI, it can be assumed that it indicates only the level over which pathological effects due to Lp(a) can occur for it cannot specifically indicate one disease.

CONCLUSION

From the discussion held on the biochemical results obtained in the study, the following facts are arrived. The reference range of Lp(a) for the study is 10.4 mg% to 26.2 mg %. Increase in Lp(a) is associated with AMI and the increase is due to inheritance of higher Lp(a) levels which should have existed even before the occurrence of the disease. Diagnostic capacity of Lp(a) is inferior to CPK if the study had been undertaken during the acute phase of AMI. Above 28 mg%, Lp(a) can speed up atherosclerosis resulting in AMI. Lp(a) levels correlate positively with lipid parameters TC and LDL-C in AMI.

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