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Serum Lipoprotein (a) Measurement in Myocardial Infarction – Are Second Thoughts Necessary?

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Abstract:

Myocardial Infarction (MI) is becoming a major public health problem in India. Early onset of coronary artery diseases and MI in Indians does not appear to be due to well known traditional risk factors alone. Investigations in many centres in the recent past have suggested that Lipoprotein (a) [Lp(a)] concentration in serum could be a powerful risk factor for MI and coronary artery disease. In the present study, association of Lp(a) with MI was investigated. Since Lp(a) in serum is known to elevate transiently during acute illness, the study was designed to estimate Lp(a) at its baseline level. Serum samples of 61 subjects with history of myocardial infarction were analysed for Lp(a). This formed the MI case group. Serum samples from age- and gender-matched subjects without any history of MI formed the control group. Baseline Lp(a) level in female cases (n=11) was significantly higher compared to controls (n=9). In male MI cases (n=50) baseline Lp(a) level were higher in cases compared to controls(n=34), but the difference was not significant. Observations made in this study fail to emphasize the utility of serum Lp(a) level in the risk assessment of MI.

Key words: Lipoprotein (a), Myocardial Infarction, Indians

Introduction

'It has been predicted that coronary artery disease might become the most prevalent disease in India by the year 2020 due to the rapid changes in demography and life styles consequent to economic development[1]. Lipoprotein (a) [Lp(a)] is perhaps one of the most important genetic factors associated with myocardial infarction. Lp(a) is a variant form of Low Density Lipoprotein (LDL) consisting of apoB-100 as well as unique apoprotein-apo(a)[2]. Lp(a) like LDL possess cholesterol ester, triacylglycerol, cholesterol, phospholipids, and a closely associated protein apo B-100 which can bind to LDL receptor. However, Lp(a) differs from LDL in containing an extra apoprotein termed apo(a). It is this apo(a) which is a giant mutant of plasminogen. Lp(a) acts as a competitive inhibitor for the action of plasminogen and prevents fibrinolysis. Lp(a) thereby acts as a dual pathogen which is both atherogenic due to its similarity with LDL and thrombogenic due to apo(a)'s structural resemblance to plasminogen[3].

Epidemiological studies of coronary heart disease and blood concentrations of Lp(a) have yielded apparently conflicting results, ranging from a strongly positive association to no association at al[4-6]. Cross sectional studies indicate that the distribution of Lp(a) concentration varies among racial and ethnic groups. So generalising the findings from one study population to another may be inappropriate[7-9]. While a few studies have indeed been carried out in India to see for a correlation between elevated Lp(a) levels and severity and extent of coronary heart disease; there is still an imperative need for more studies in different parts of the world to assess the role of Lp(a) as a risk factor in Myocardial Infarction (MI). Several studies indicate that Lp(a) levels elevate transiently during acute conditions[10]. The question then arises whether the elevation of Lp(a) observed in MI cases was a cause or an effect of MI.

Hence this study was carried out to see for the correlation of Lp(a) with MI in this part of south India comprising of the coastal Karnataka region. Moreover, the study was designed keeping in mind the acute phase response of Lp(a).

Materials

The hospital registry of Kasturba Hospital, Manipal, India, for the years 2001 and 2002 was screened for the residential addresses of MI patients who had been admitted and treated in the hospital during those two years. The patients listed in the hospital registry as I-21 according to the International Statistical Classification of Diseases and related health problems (10th Revision Vol-1) of WHO 1992, Geneva, were selected. The patients had no other complications involving renal, hepatic, or cerebrovascular system. The patients were contacted by mail through personal letters describing the objective of the study and participation was solicited. Informed consent was obtained from all the volunteers. The fasting blood samples were obtained after a minimum time period of 4 weeks had elapsed after the MI episode. This meant that only the survivors of MI were the cases in the study. Appropriate age and sex-matched individuals formed the control group.

Methods

All the blood samples were collected after overnight fasting. Serum was separated out within 2 hours of blood collection. Serum Lp(a) was estimated by automated immunoturbidimetric assay. Specific anti-Lipoprotein (a) antibodies react with antigen in the sample to form antigen-antibody complex which is determined turbidimetrically after agglutination at 340nm. Lp(a) [Tina-quant (a)] reagent kit was from Roche Diagnostics, Mannheim, Germany (Cat No. 1660390). Hitachi 912 system automatically calculates the lipoprotein (a) concentration of each sample. The method has a measuring/reportable range from 6-160mg/dl. Statistical analysis was performed using SPSS statistics program. Student t- test was used for comparison between the cases and controls. P value <0.05 is considered significant.

Results

A total of 196 cases of MI were contacted, out of which 61 patients (50 males and 11 females) agreed and obliged to provide their fasting blood samples. Forty three (43) healthy subjects of corresponding age (34 males and 9 females) without any symptom or history of MI formed the control group. The results of the tests in case of females and males were analysed separately.

Serum Lp(a) in female MI cases vs controls: Female MI cases (n=11) group was compared with control group (n=9). 10 of the 11 cases were more than 50 years of age. The results are given in Table 1. Serum Lp(a) concentration in general exhibited a positive skew as observed in different studies around the world. The levels ranged between 17

and 236 mg/dl in cases, and from 6 to 55mg/dl in controls. Serum Lp(a) concentration was found to be significantly higher in cases compared to the controls (p-value <0.01).

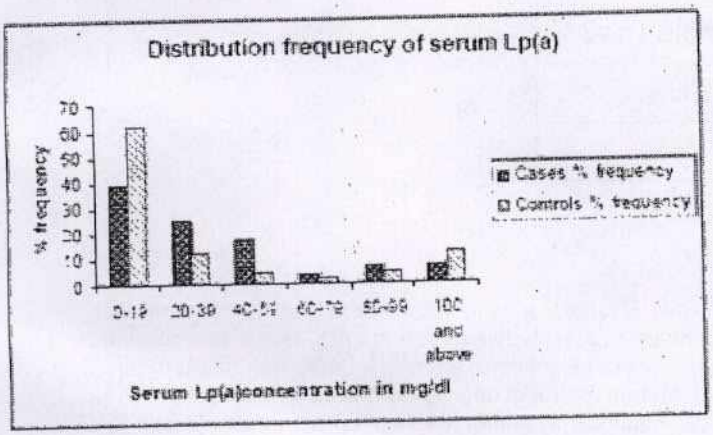
Serum Lp(a) and lipid profiles in male MI cases vs controls:

Male MI (n=50) group was compared with the control group (n=34). The results are shown in Table 1. Serum Lp(a) level in MI cases as well as controls showed skewed distribution pattern. Among the cases Lp(a) levels ranged from 0-281 mg/dl and in controls from 0 to 137 mg/dl. The mean Lp(a) level though higher in cases than in controls was not statistically significant.

Table-1: Serum Lp(a) Levels in Male and Female Cases vs Controls

Gender	Fasting serum Lp (a) levels in mg/dl Mean ±SD	
	CONTROLS	CASES
Females	15.7 ± 15.5 (n=9)	75.2 ± 64.3* (n=11)
Males	35.65 ± 41.09 (n=34)	42.14 ± 56.30 (n=50)

* p-value 0.01- significant



Distribution frequency of serum Lp(a):

The percentage frequency distribution of serum Lp(a) in cases and controls is shown in Figure 1. There is more aggregation of controls in the lower concentration ranges. 62% of controls had Lp(a) levels below 20 mg/dl and only 39% of cases had Lp(a) levels below 20 mg/dl.

Lipoprotein(a), a lipoprotein subclass, is a risk factor for coronary heart disease (CHD), cerebrovascular disease (CBD), atherosclerosis, thrombosis, and stroke and other vascular diseases. It is assembled in the blood from low density lipoprotein (LDL) molecules and glycoprotein molecules called apolipoprotein-a (apo-a). Plasma apo-a is secreted by the liver. Lipoprotein(a) recruits inflammatory cells through interaction with Mac-1 integrin. The mechanism and sites of Lp(a) catabolism are unknown.

High Lp(a) predicts risk of early atherosclerosis similar to high LDL, but in advanced atherosclerosis, Lp(a) is an independent risk factor not dependent on LDL. Lp(a) then indicates a coagulant risk of plaque thrombosis. Apo(a) contains domains that are very similar to plasminogen (PLG). Lp(a) accumulates in the vessel wall and inhibits

binding of PLG to the cell surface, reducing plasmin generation which incre[illegible]lotting. This inhibition of PLG by Lp(a) also promotes proliferation of smooth muscle cells. These unique featu[illegible] Lp(a) suggest Lp(a) causes generation of clots and atherosclerosis.[1]

Lp-a concentrations may be affected by disease states, but are only moderately affected by diet, exercise, and other environmental factors. Lipidreducing drugs have no effect on Lp(a) concentration. Lp-a is genetically linked with concentrations varying over one thousandfold, from < 0.2 to > 200 mg/dL. African populations have Lp-a concentrations severalfold higher than Caucasians and Asian populations. For risk categorization desirable levels are < 14 mg/dL [Borderline risk: 14 - 30 mg/dL; High risk: 31 – 50 mg/dL; Very high risk: > 50 mg/dL] (Ed)

Caplice, N M et al. Lipoprotein (a) binds and inactivates tissue factor pathway inhibitor. Blood 2001; 98 (10): 2980-2987. Christian Wilde. Hidden Causes of Heart Attack and Stroke, 2003; pages 182-3.

Julius Torelli. Beyond Cholesterol, 2005; page 91.

Odds ratio for Lp(a):

In many epidemiological studies, Lp(a) level of 30 mg/dl is considered as the normal cut-off point in risk assessment11. We categorized each group based on this cut off point and the results are given in Table 2. This distribution pattern does not indicate any difference between controls and male MI cases.

Table 2: Odds Ratio for Lp(a) with a Cut-off Point of 30 mg/ dl

Lp(a) level mg /dl	MI cases (n=50)	Controls (n=34)
< 30 mg/dl	30 (60%)	20 (59%)
≥ 30 mg /dl	20(40%)	14 (41%)

Discussion

Table 3 summarizes the observations on serum Lp(a) from several laboratories in India. In the studies from India, Bahl et al[12] and Ramachandran et al[13] observed no significant association between serum Lp(a) levels and coronary artery disease. Few other case-control studies also failed to note significant correlation[14,15]. Lp(a) was found to be significantly higher in young (<45 years of age) patients with MI and their first degree relatives compared to controls[16]. Gupta et al[17] and Geethanjali et al[18] have observed significantly higher levels of Lp(a) in patients with CAD compared to controls.

The LP(a) levels in the control group as well as patient groups from different laboratories are comparable considering the wide variations in the level of Lp(a) and the highly skewed distribution. Yet in our study Lp(a) of MI patients did not significantly differ from that of the controls. This study was carried out in a medical centre located in rural part of the country. Possibility of difference in samples from rural and urban population needs to be kept in mind and studied further. Although diet and physical inactivity are not known to influence the Lp(a) concentration, it is possible that these may minimize the effects of Lp(a)[19].

Craig et al[20] analysed the results of several prospective studies carried out to assess Lp(a) as risk factor for ischemic heart disease and noted at least six fold variation in reported Lp(a) concentration, which clearly indicates a great need for standardisation and inter - laboratory communication and quality control. In the case of Lp(a), there is insufficient separation between concentration from cases and controls to support the use of Lp(a) as a screening test for MI risk in general population. In a report of the NHLBI workshop on Lp(a) and cardiovascular disease, Marcovina[21] emphasises that screening for Lp(a) is recommended in individuals with increased risk of CVD and not in the general population. A comparative study of novel risk factors for atherosclerosis by Ridker et al[22] revealed that there is nonsignificant base line elevations of Lp(a).

Most of the reports emphasize that serum Lp(a) concentration is independent of other CAD risk factors[23]. However, recent investigations and some of the earlier reports have noted evidences to suggest that disease risk due to high Lp(a) is dependent on concomitant presence of other risk factors such as high total cholesterol, high LDL – cholesterol, increased apo-B and low HDL – cholesterol[24]. Even if the Lp(a) levels as a risk indicator are assessed, at present there is no well established treatment to lower Lp(a) levels. However, in people with higher levels, Adult Treatment Panel (ATP-III) of National Cholesterol Education Program has recommended a more stringent treatment for dyslipidemias [25].

Table 3: Serum Lp(a) levels in cases vs controls from different studies in India

Studies	Lp(a) mg/dl CONTROL	Lp(a) mg/dl CASES
Gupta et al 199617	15.07 ± 14.6	28.83 ± 22.1
Mohan et al 199826	19.4 (2.6)	24.6 (3.0)* ¶
Gupta et al 200027	6.68±3.4	11.95 ± 2.8 *¶
Vasisht et al 200028	24.27 ± 24.9	40.9 ± 34.0*
Gambhir et al 200029	20.3 ± 17.0	35.0 ± 32.4*
Ramachandran et al 200113	20.0 (3.4)	23.0 (3.3) ¶
Isser et al 200116	9.28 ± 2.59	22.24 ± 5.4*
Geethanjali et al 200218	21.4 ± 12.8	33.4 ± 26.1*
Present study	35.65 ± 41.09	42.14 ± 56.3

* Significantly different ¶ These values are geometric mean. All others are Mean ± SD

Conclusion

Serum Lp(a) concentration in controls and MI cases shows a highly skewed distribution pattern. Lp(a) concentration was significantly higher only in the female MI cases and not in the male MI cases. The sample size of the female MI case group is small to extrapolate the finding to the general population. However, the Lp(a) levels estimated in the current study reflect the base line levels of Lp(a). Further studies employing larger sample size is required to confirm the current conclusion.

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References

1. Mohan V, Deepa R, Rani SS, Premlatha G. Prevalence of coronary artery disease and its relationship to lipids in a selected population in south India: CUPS No 5. J. Am Coll Cardiol. 2001; 38:682-687
2. Berg K. A new serum type system in man- the Lp-system. Acta Pathol Microbiol Scand. 1963; 59: 369-89
3. Utermann G. The mysteries of lipoprotein (a). Science 1989; 246: 904-910
4. Danish J, Collins R, Peto R. Lipoprotein (a) and coronary heart disease: Meta analysis of prospective studies. Circulation. 2000; 102:1082-1085
5. Gurewich V, Mittleman M. Lipoprotein (a) in coronary heart disease: Is it a risk factor after all? JAMA 1994; 271: 1025-1026
6. Barnathan ES. Has lipoprotein 'little' (a) shrunk? JAMA 1993; 270: 2224-2225

7. Srinivasan SR et al.Racial (black- white) differences in serum lipo[illegible](a) distribution and its relation to parental myocardial infarction in children. Circulation. 1991;84:160
8. Parra HJ et al. Black- white differences in serum Lp(a) lipoprotein leve[illegible]lin Chim Acta.1987; 167: 27-31
9. Guyton JR et al. Relationship of plasma lipoprotein Lp(a) levels to race and to apolipoprotein B. Arteriosclerosis.1985;5: 265- 272
10. Craig WY, Ledue T. Lipoprotein (a) and the acute phase response. Clin Chem. Acta 1992;210: 231-32
11. Hajjar KA, Nachman RL. The role of lipoprotein (a) in atherogenesis and thrombosis. Annu Rev Med. 1996; 47:423-42
12. Bahl VK, Vasisht S et al. Association of plasma lipoproteins with angiographically defined coronary artery disease. Indian Heart Journal. 1995;47: 244-247
13. Ramachandran A, Sathyamurthy I, et al. Risk variables for coronary artery disease in Asian Indians. Amer.J.Cardiol.2001;87: 267-271
14. Jauhiainen M et al. Lipoprotein (a) and coronary heart disease risk: a nested case-control study of the Helsinki Heart Study participants. Atherosclerosis. 1991; 89:59-67
15. Ridker PM, Hennekens CH and Stampfer MJ. A prospective study of lipoprotein (a) and the risk of myocardial infarction. JAMA.1993; 270 : 2195-99
16. Isser HS, Puri VK et al. Lipoprotein (a) and lipid levels in young patients with myocardial infarction and their first degree relatives. Indian Heart J. 2001;53: 463-466
17. Gupta R, Vasisht S, Bahl VK, Wasir HS. Correlation of lipoprotein (a) to angiographically defined coronary artery disease in Indians. Intern J Cardiol. 1996; 57:265-270
18. Geethanjali FS, Jose VJ and Kanakasabapathy AS. Lipoprotein (a) phenotypes in South Indian patients with coronary artery disease. Indian Heart journal. 2002; 54:50-53
19. Bhatnagar D, Anand IS et al. Coronary risk factors in people from the Indian subcontinent living in west London and their siblings in India. Lancet.1995; 345:405-09
20. Craig WY, Neveux LM et al. Lipoprotein (a) as a risk factor for ischemic heart disease: metaanalysis of prospective studies. Clin Chem. 1998; 44: 2301-06
21. Marcovina SM, Koschinsky ML, Albers JJ and Skarlatos S. Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein(a) and Cardiovascular Disease: recent advances and future directions. Clin Chem. 2003, 49:1785-96
22. Ridker PM, Stampfer MJ and Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA. 2001;285 :2481
23. Lippi G and Guidi G. Biochemical risk factors and patient's outcome: the case of lipoprotein(a). Clin. Chim. Acta. 1999,280:59-71
24. Cantin B, Gagnon F, Moorjani S et al.Is lipoprotein(a) an independent risk factor for ischemic heart disease in men? The Quebec Cardiovascular Study. J Am Coll Cardiol. 1998; 31: 519-525
25. Executive summary of the third report of the National cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel –III). JAMA. 2001;285: 2486-2496
26. Mohan V Deepa R et al. Lipoprotein (a) is an independent risk factor for coronary artery disease in NIDDM patients in south India. Diabetes care,1998;21:1819-23
27. Gupta R, Kastia et al. Lipoprotein (a) in coronary heart disease- a case-control study. Indian Heart Journal.2000; 52: 407-410
28. Vasisht R, Gulati R et al. Apolipoprotein(a) polymorphism and its association with plasma lipoprotein(a) levels: a north Indian study. Indian Heart J. 2000;52:165-170
29. Gambhir JK, Kaur H, Gambhir DS and Prabhu KM. Lipoprotein (a) as an independent risk factor for coronary artery disease in patients below 40 years of age. Indian Heart journal. 2000,52:411-415