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Original Research Article

Study on association of serum lipoprotein(a) with coronary artery disease

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ABSTRACT

Background: Most studies of lipid-lowering therapy for the prevention of coronary heart disease (CAD), focused on lowering low density lipoprotein cholesterol and non-HDL cholesterol. Other dyslipidemias, such as an elevated level of lipoprotein(a), also may promote atherosclerosis, establishment of relationship between lipoprotein(a) excess and risk for CAD, interventions directed toward altering these have only infrequently been evaluated in clinical trials. Objectives was to study the association of raised serum lipoprotein(a) in coronary heart disease.
Methods: This study was conducted in 50 patients of CAD and 50 people as control group. All patients underwent a standard clinical examination and a blood draw for a lipid profile and lipoprotein(a) assay. Pearson chi-square test was used to assess the statistical significance.
Results: Lipoprotein(a) value of more than 30 mg/dl is considered as elevated. In case group 19 patients (38%) were showed elevated lipoprotein(a) and in control group these were 9 patients (18%). p value is 0.026. It shows elevated lipoprotein(a) is statistically significant with the relative risk of 2.79.
Conclusions: The association of elevated lipoprotein(a) with CAD was statistically significant. Higher lipoprotein(a) levels were observed in patient with family history of premature CAD.

Keywords: Coronary heart disease, Dyslipidemias, Lipoprotein

INTRODUCTION

Coronary artery disease (CAD) is the major cause of death in the world today.[1] Many factors are responsible for causing CAD, but it is notable that 5 to 10 percent of CAD patients have none of the known risk factors.[2]

Risk factor modification is an integral part of the management of patients who have or are at risk for cardiovascular disease. In addition to established cardiovascular risk factors, clinical research has identified more than 100 other conditions that may be associated with an increased risk for cardiovascular disease. Almost 25% of patients with premature cardio- vascular disease do not have any established risk factors.[3] As a result of reductions in morbidity and mortality attributable to hypertension, smoking, and dyslipidemia, the relative contribution of new risk factors to the total burden of cardiovascular disease is likely to increase.[4-6] Significant associations exist between established and new risk factors, and better understanding of new risk factors may shed light on the pathogenetic mechanisms of established risk factors. On the basis of a growing body of evidence, the 1996 Bethesda conference acknowledged left ventricular hypertrophy, hyperhomocysteinemia, lipoprotein(a) excess, hypertriglyceridemia, hyperfibrinogenemia (among other thrombogenic

factors), and oxidative stress as possible risk factors for CAD.

Lp(a) levels correlate with both early and advanced atherosclerosis, severity, extent and progression of atherosclerosis and all complications of CAD including re-stenosis following percutaneous transluminal angioplasty, stent and bypass surgery.[7] Lipoprotein(a) excess increases the risk of premature CAD 3 to 100 fold depending on the absence or presence of concomitant risk factors.[8]

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.[9-11]

Whom to screen

Lp(a) should be measured once in all subjects at intermediate or high risk of CVD/CHD who present with:

- premature CVD,
- familial hypercholesterolaemia,
- family history of premature CVD and/or elevated Lp(a),
- recurrent CVD despite statin treatment,
- ≥3% 10-year risk of fatal CVD according to the European guidelines,[12]
- ≥10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines.[13]

Aim of the research work was to study the association of raised serum lipoprotein(a) in patients with coronary heart disease and to study the role of raised serum lipoprotein(a) levels as risk factor when compared to other known risk factors in coronary heart disease.

METHODS

This was a case controlled study. This study was conducted in 50 patients of coronary heart disease. They were selected as outpatient and inpatients in the Department of Medicine, Meenakshi Medical College Hospital and Research Institute during the period of February 2018 to August 2018. This study also included 50 people as control group.

Inclusion criteria

Coronary heart disease patients above 16 years of age were selected. As per 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) CHD is defined as symptomatic ischemic heart disease, including myocardial infarction, stable or unstable angina, demonstrated myocardial ischemia by non invasive testing, and history of coronary artery procedures.

Exclusion criteria

Patients with renal impairment, pregnancy, hypothyroidism, nephrotic syndrome, cancer and patients on drugs like sodium valproate, carbamazepine, cyclosporin, methotrexate, theophylline, levodopa, metformin, estrogen (OCP), INH, fibrates and niacin were excluded.

Study population

Cases

A total of 50 patients were recruited for the study based on clinical, biochemical and ECG evidence. An informed consent was taken from the patient. They included 38 males and 12 females. Patients with confirmed diagnosis of coronary heart disease and satisfying the inclusion and exclusion criteria with no previous ischemic heart disease were included in the study group.

Controls

Around 50 normal individuals symptomatically and electrocardiographically were selected as control.

Data collection

All patients (cases and controls) underwent a standard clinical examination by nurses and physicians, which included measurements of height, weight, waist-hip ratio, blood pressure, and an overnight fasting blood draw for a lipid profile. Patients also received dietary and smoking counselling when necessary. Individuals also completed a questionnaire that incorporated numerous risk related issues, including a history of hypertension, family history, cholesterol medication use, and diabetes, in women, menopausal status and use of hormones. Patients were classified as either never- or ever-smokers. Hypertension was defined as a blood pressure above 140/90mmHg, a history of hypertension, or the use of antihypertensive medications. Diabetes mellitus was diagnosed if the patient was using insulin or an oral hypoglycemic agent or reported a history of diabetes mellitus.

Biochemical analysis

Following investigations were done in all patients in the study, and the control groups.

- Early morning fasting samples of blood were collected and sent for lipid profile, lipoprotein(a)
- Complete blood count

- Random blood sugar, urea, creatinine
- CKMB
- Troponin-T
- ECG 12 lead, if necessary right side and posterior leads
- X-ray chest PA view
- 2D Echocardiography.

Fasting total cholesterol, HDL-C, LDL-C, and triglyceride concentrations in the blood sample drawn at the same time as the sample for measurement of Lp(a) were measured in all subjects after six weeks of acute coronary event. Lipoproteins were measured in serum after a 12-hour fast.

Lp(a) assay

Serum Lp(a) estimation was performed using quantitative latex-enhanced immunoturbidimetric test using Human Lp(a) kit. Values less than 5mg/dL are undetectable. Short-term post-myocardial infarction increases in Lp(a), believed to be only transient, return to normal levels within 1 month.

Protocol

Venous blood samples were obtained from study population by trained medical or senior nursing staff from antecubital vein. Blood was transferred into containers containing EDTA for lipoprotein assay. Within 15mins of collection, platelet poor plasma was obtained by centrifugation at room temperature for 15mins at 3000rpm and then transferred to a -80°C freezer. Blind analysis of all samples was performed in batches at completion of sample collection.

Statistical analysis

The comparison of risk factors in case and control group was done by the t- test for equality of means. All values were calculated as mean±standard deviation. Pearson chi-square test was used to assess the statistical significance. P value of less than 0.01 indicates highly significant and value of less than 0.05 indicates significant. The odds ratio is used to estimate the relative risk.

RESULTS

The case group comprised patients with age ranging from 34 to 85, and a mean age of 55.96. In the control group age ranged from 34 to 70, with a mean age of 51.50. A male preponderance of 70% was seen in the case group but was not of statistical significance. There were no gender differences in Lp(a) levels in both patients and controls as similar with Pedreno et al. But Lp(a) Better assessor of coronary heart disease risk in South Indian population study by Rajasekhar D et al showed higher Lp(a) levels in females when compared to males in patients and is in agreement with other reports. 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 and presence of menopausal status in women with CHD or may be due to discrepancy in sample size.

Table 1: Comparison of lipoprotein(a) between case and control group.

			Case	Control	Total
Lipoprotein A	<30	Count	31	41	72
		%	43.1%	56.9%	100%
	>30	Count	19	9	28
		%	67.9%	32.1%	100%

Table 2: Lipoprotein(a) between case and control group chi-square test.

	Value	df	p-value
Pearson chi square	4.960	1	0.026
N of valid cases	100		

Table 3: Lipoprotein(a) with family history of premature CHD.

		Family history -no	Family history -yes	Total
Lipoprotein a	<30- Count	30	1	31
	% within lipoprotein a	97.8%	3.2%	100%
	%within family history	88.2%	6.3%	62%
	>30 - count	4	15	19
	% within lipoprotein a	21.1%	78.9%	100%
	%within family history	11.8%	93.8%	38%

Lipoprotein (a) value of more than 30 mg/dl is considered as elevated. In case group 19 patients (38%) were showed elevated lipoprotein (a) and in control group these were 9 patients (18%) (Table 1). p value is 0.026. It shows elevated lipoprotein (a) is statistically significant in case group with the relative risk of 2.79 (Table 2).

Family history of premature CHD was present in 16 patients in case group (Table 3) and 5 in control group.

Pearson chi-square test shows p-value of 0.008 (Table 4) and the association is statistically significant. LDL-C value of more than 130mg/dl was observed in 18 patient (36%) when compared to 1(2%) in control group. And value of 100 to 129mg/dl was observed in 23 (46%) when compared to 31 (62%) in control group. Value of 90 to 99mg/dl was observed in 3 (6%) when compared to 12 (24%) in control group. Value of less than 90mg/dl was observed in 6 (12%) when compared to 6 (12%) in control group. Mean value of LDL-C is 122.64 in case group and 106.48 in control group (Table 5). T-test for equality means shows p-value of <0.001 and is highly significant (Table 6).

Table 4: Lipoprotein(a) with family history of premature CHD Chi-square test.

	Value	df	p-value
Pearson chi square	11.79	1	0.008
N of valid cases	50		

Table 5: Comparison of LDL-C between case and control group.

	N	Mean	SD	SEM
LDL case	50	122.64	26.638	3.767
Control	50	106.48	12.144	1.717

Table 6: LDL-C t-test for equality of means.

						95% confidence interval of the difference	
LDL	t	df	p-value	Mean difference	Std. error difference	lower	upper
	3.903	98	0.000	16.16	4.140	7.944	24.376

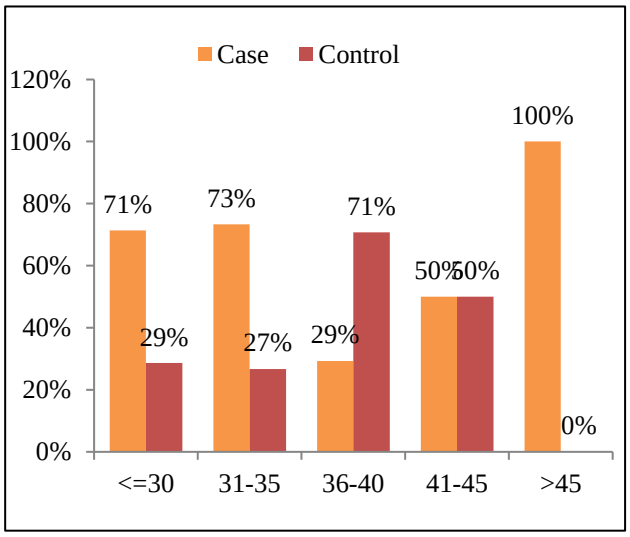

Figure 1: Comparison of HDL-C between case and control group.

HDL-C value of less than 40mg/dl was observed in 28 patient (56%) in case group when compared to 35 (70%) in control group. And value of more than 40 mg/dl was observed in 22 (44%) when compared to 15 (30%) in control group. Mean value of HDL-C is 39.10 in case group and 38.88 in control group. T-test for equality means shows p-value of 0.842 and is not significant (Figure 1). The mean value of triglyceride in case group is 115.52mg/dl and 106.50 in control group. And the association in between these two is not significant (Figure 2). The mean value of total cholesterol in case group is 160.34mg/dl and 171.98 in control group. And the association in between these two is not statistically significant (Figure 3).

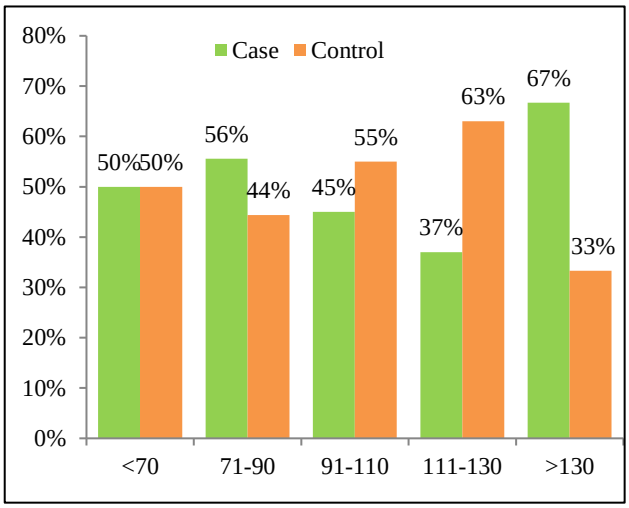

Figure 2: Comparison of TGL between case and control group.

Sedentary life style was present in 25 patients in case group and 12 in control group. p-value is 0.007 and the association is statistically significant. In case group 19 patients (38%) were alcoholics when compare to 12 (24%) in control group. p-value is 0.130 and the association is not statistically significant. Diabetes was present in 22 (44%) patient in case group and 8(16%) in control group. p-value is 0.002 and the association is statistically significant.

In case group 22 patients (44%) were smokers when compare to 13 (26%) in control group. p-value is 0.059 and the association is not statistically significant. Hypertension was present in 26 (52%) patient in case

group and 5 (10%) in control group. p-value is <0.001 and the association is highly significant. No significant variation in Lp(a) values when compared with hypertension in patients and control. Weak positive correlation of Lp(a) and systolic blood pressure and LDL-C was observed in one study. There was no positive correlation in between Lp(a) with LDL-C similar with the study of Eritsland et al. But other studies reported positive significant association of Lp(a) with LDL-C. Lp(a) levels showed significant correlation with CAD as similar with earlier studies.

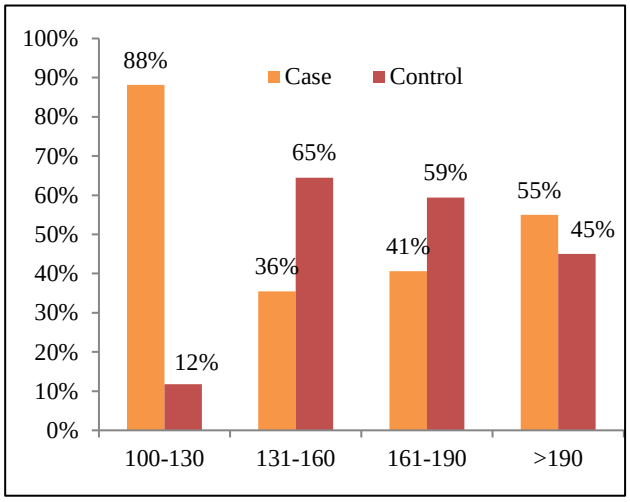

Figure 3: Comparison of TC between case and control group.

No significant variation in Lp(a) values when compared with diabetes, smoking, alcoholism, and lipid profile. Parameters like BMI and waist to hip ratio were not statistically associated with levels of lipoprotein(a).

DISCUSSION

Lipoprotein(a) concentration is, however, a relatively modest coronary risk factor, being only about one quarter as strong overall as non–HDL cholesterol, although Lp(a) may become proportionally more important to CHD at very high concentrations owing to its potentially curvilinear risk relationship. Because associations of higher Lp(a) concentration with CAD are similar at different levels of non- HDL cholesterol, the absolute benefits of cholesterol lowering should be greater if Lp(a) concentration is high.

Consequently there has been intensive research to identify new risk factors that will enhance predictive power in individuals. These newer factors can be called emerging risk factors. For present purposes, these can be conveniently divided into three categories: lipid risk factors, nonlipid risk factors, and subclinical atherosclerotic disease. In this present study one of the emerging lipid risk factor, lipoprotein(a) was selected and the association of this with coronary heart disease was tested along with comparison of other established risk factors of CAD. Several studies report a strong association between Lp(a) levels and CAD risk.[14-17] Indeed, a recent meta-analysis of reported prospective studies supports an independent predictive power for elevated Lp(a).[18]

In the present study there is no positive correlation in between Lp(a) and LDL. In addition, concomitant elevations of Lp(a) and LDL cholesterol have been reported to have synergy in elevating risk in both men and women for CAD. On the basis of these studies, some authorities hold that an elevation of Lp(a) is an independent risk factor for CAD. It must be noted nonetheless that several prospective studies do not confirm independent prediction.[19,20] Thus, the quantitative contribution of elevated Lp(a) to CAD risk beyond the major risk factors is uncertain. This uncertainty extends both to individuals and populations; in the latter, the frequency of elevated Lp(a) is not as high as for the major risk factors.

Several possible mechanisms have been proposed to explain the association between Lp(a) and vascular disease. First, it has been suggested that Lp(a) plays a part in the initiation, progression, and subsequent rupture of atherosclerotic plaque.[21] Second, because of the structural homology of apoprotein(a) and plasminogen, Lp(a) may compete with, bind, and inhibit the thrombolytic activity of tissue plasminogen; Lp(a) could therefore have a thrombogenic effect by its interference with intrinsic fibrinolysis.[22] Third, Lp(a) has been associated with endothelial dysfunction.[23] Fourth, Lp(a) activates monocytes, colocalizes with plaque macrophages, stimulates smooth-muscle cells, and could induce inflammation.[24]

Recent recommendations state that lipoprotein(a) screening is not warranted for primary prevention and assessment of cardiovascular risk at present but that lipoprotein(a) measurements can be of use in patients with a strong family history of cardiovascular disease or if risk of cardiovascular disease is judged intermediate on the basis of conventional risk factors.[25] In addition to measurement difficulties, a number of factors contribute to lipoprotein(a) levels not being incorporated into routine cardiovascular risk assessment presently. First, there are no effective drugs that selectively reduce plasma levels of lipoprotein(a). The only well known means of lowering lipoprotein(a) levels is high doses of niacin, which affects the levels of many other lipoproteins and is not universally tolerated.[26] No studies have yet documented a reduction in IHD in response to niacin treatment in individuals with elevated lipoprotein(a) levels. Second, the mechanism of action of lipoprotein(a) as a promoter of cardiovascular events is not clear. Finally, plasma levels of lipoprotein(a) have failed to alter the receiver operating characteristic curve independently of traditional risk factors when used for risk prediction.[27] Measurements of lipoprotein(a) levels might help to identify as yet unidentified high-risk

individuals who could benefit from other aggressive, prophylactic measures, including statins directed at elevated cholesterol levels. Indeed, the influence of lipoprotein(a) in causing MI and IHD is muted with substantial cholesterol reductions in hypercholesterolemic patients.[28]

Prospective studies, in contrast, revealing both positive and negative associations. For example lipid research clinics follow-up trial and the Framingham offspring cohort revealed a significant risk of CAD for an Lp(a) value of 30mg/dL, the Physicians' health study did not show any significant association between Lp(a) and cardiac events. A study of lipoprotein(a) as a cardiovascular risk factor: current status by Nordestgaard BG et al shows that the robust and specific association between elevated Lp(a) levels and increased cardiovascular disease/coronary heart disease (CHD) risk, together with recent genetic findings, indicates that elevated Lp(a), like elevated LDL cholesterol, is causally related to premature CVD/CHD. The association is continuous without a threshold or dependence on LDL- or non-HDL-cholesterol levels

A study on lipoprotein (a): better assessor of coronary heart disease risk in south indian population by D. Rajasekhar et al shows Low levels of total-C and HDL-C observed in patients when compared to controls. Low levels of HDL-C are reported to increase the risk of CAD even when total cholesterol is not elevated. But in this present study HDL-C levels are not correlated with CAD. Increased total-C and LDL-C levels are reported in patients than in controls. In this study high levels of LDL-C were observed in patients against controls.

Lp(a) increases the risk of coronary events strongly depending on the presence of additional coronary risk factors, it is imperative to strictly control additional risk factors in individuals with elevated Lp(a). In agreement with this concept, lowering of LDL cholesterol with colestipol or simvastatin was previously found to reduce coronary events in individuals with elevated Lp(a).

Substantial modification of Lp(a) concentration has been difficult to achieve without pharmacological agents. Niacin and certain inhibitors of cholesteryl ester transfer protein can reduce Lp(a) by about 20% and about 40%, respectively. Contradictory findings have been reported about the effect of statins on Lp(a) concentration, and it remains uncertain whether statin use attenuates the CAD risk associated with Lp(a) concentration. Large randomized trials of niacin and cholesteryl ester transfer protein inhibitors in the secondary prevention of CAD are in progress. Such studies may not, however, enable causal inferences because, in addition to Lp(a) lowering, these agents increase HDL cholesterol and decrease LDL cholesterol and triglyceride concentrations. Under a wide range of circumstances, there are continuous, independent, and modest associations of Lp(a) concentration with the risk of CAD and stroke that appear exclusive to vascular outcomes.

CONCLUSION

The association of elevated lipoprotein(a) with CAD was statistically significant, but at the same time this is not that much strong when compare to the elevated LDL-C.

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