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Original Research Article

Association of LpPLA2 with coronary artery disease a hospital-based case control study

Rajesh Thachathodiyil[1], Anugrah Nair[2], Rajiv Chandrasekhar[1], Natarajan Kumaraswamy[1], Vijayakumar Maniyal[1], Praveen G Pai[1], Navine Mathew[1], Harikrishnan S Madhavankutty[1], Saritha Sekhar[1], Hisham Ahmed[1], Jofy Paul[3], Riji Thomas[3], Aneesa Ayoob[4], Chandrasekhar Janakiram[4], Jaideep C Menon[1,*]

[1]*Dept. of Adult Cardiology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India*
[2]*Dept. of Cardiology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India*
[3]*Agappe Diagnostics, Pattimattom, Kerala, India*
[4]*Dept. of Public Health Dentistry, Amrita School of Dentistry, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India*

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ABSTRACT

Background: Coronary artery disease (CAD) in Asian-Indians is characterised by an earlier onset and more severe disease when compared to Western populations. It is estimated that about 20% of patients presenting with an acute coronary syndrome do not have any of the conventional risk factors for CAD.
Aims: To assess the risk posed by each of the newer risk factors; alongside conventional risk factors namely diabetes, hypertension, dyslipidaemia for coronary artery disease and to compare the relative risk in a case-control design.
Study Setting: Department of Cardiology, XXX Institute of Medical sciences (XXX).
Study Design: Case control study design.
Methods: Cases are as any individual with coronary artery disease and controls included patients with non-coronary conditions. Dependant variable: coronary artery disease (CAD); Independent variables: Lp PLA2, Lp(a), Apo(a), Apo(b), Ratio (Apo B/Apo A); Other predictors- diabetes mellitus, hypertension, dyslipidaemia, tobacco use
Statistical Analysis used: Categorical variables were presented as frequencies and percentages. Chi-square test and binary logistic regression analysis was used to study the comparison and association of the categorical risk factors with the disease status, respectively. Software used was SPSS version 20.0.
Results: A total of 253 participants aged between 19 and 90 years; 140 cases and 113 controls were enrolled in this study. Except for the hs-CRP level, alcohol consumption and LDL, all the other risk factors were seen significantly associated with the coronary artery disease; dyslipidaemia (10.8, 95% CI 3.29-35.37), gender- male (4.68, 95% CI 2.12-10.30), diabetes mellitus (3.3, 95% CI 1.6 -6.77), lipoprotein(a) more than 30mg% (2.34, 95% CI 1.06-5.15) and hypertension (2.48, 95% CI 1.14-5.39).
Conclusion: Conventional risk factors namely diabetes, hypertension and dyslipidaemia showed a statistically significant association with CAD while from among the biochemical markers the association was statistically significant only for Lp(a) when compared both between cases and controls and also in cases < age 50 years. The other biochemical risk factors namely Lp-PLA2, Apo(A1) and Apo(b) showed a weak degree of association with CAD.
Key Messages: In the present study we analyse the role of inflammatory mediators of CAD (hs-CRP, Lp-PLA2), pro-thrombotic markers [Lp(a)] alongside the lipid fractions apoB, apo A and their ratio to assess which of these biochemical markers predisposed one to CAD through assessment of the relative risk.

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1. Introduction

Cardiovascular disease is the leading cause of mortality worldwide, as so in India.[1] Coronary artery disease (CAD) in Asian-Indians is characterised by an earlier onset and more severe disease when compared to western populations. It is estimated that about 20% of patients presenting with an acute coronary syndrome do not have any of the conventional risk factors for CAD, especially in those < 50 years of age.[2,3]

Dyslipidaemia is one of the major risk factors for AS-CVD (atherosclerotic CVD), in which elevated levels of low-density lipoprotein cholesterol (LDL-C) is a major contributor to subsequent CVD events. In spite of numerous clinical trials having shown that reducing LDL-C levels, substantially reduces the risk of CVD suggesting a strong causality, individuals continue to have residual CVD risk and suffer from CVD events despite significant LDL-C lowering in addition to the fact that many individuals have AS-CVD with normal lipid values.[4,5] There are very likely other factors influencing atherosclerosis of which lipoprotein associated phospholipase A2 (Lp-PLA2), apolipoprotein B (apo B), apolipoprotein A1 (apo A1) and lipoprotein(a) [Lp(a)] are likely candidates especially in the young coronary artery disease (CAD) subset of patients defined as males below 55 years and females below 65 years of age having CAD.[6]

Lipoprotein-associated phospholipase A2 (Lp-PLA2), an enzyme expressed by inflammatory cells in atherosclerotic plaques, is carried in the circulation bound predominantly to LDL. Lp-PLA2 and other human A2 phospholipases (such as secretory phospholipase A2) propagate inflammation by producing precursors of arachidonic acid from membrane glycerophospholipids. Lp-PLA2 hydrolyses oxidised phospholipids to yield pro-inflammatory products that are implicated in endothelial dysfunction, plaque inflammation, formation of necrotic core in plaques, and is postulated to link oxidative modification of LDL and development of inflammatory responses in the arterial intima due to which Lp-PLA2 is considered a marker for future cardiac events. Research papers on this subject have been predominantly from the western literature and there is a lack of studies from India. With this background, it is proposed to compare LpPLA2 levels alongside other risk factors for CAD.[2,7–9]

Robust association between Lp(a) and CVD outcomes in the general population has been published in previous studies. Wealth of current evidence suggest that increased Lp(a) level is associated with a modest increase in risk of future CVD events in both general and high risk populations. Such an association of Lp(a) with CVD, is independent of LDL, reduced high density lipoproteins (HDL), and other traditional CVD risk factors.[10,11]

* *Corresponding author*.
E-mail address: menon7jc@gmail.com (J. C. Menon).

Epidemiologic studies have established an inverse relationship between plasma levels of HDL cholesterol and the occurrence of CAD, while low-density lipoprotein has been established as an atherogenic factor. Apo A-1 is the major protein component of high-density lipoprotein cholesterol (HDL-C) which is a 243 amino acid long peptide, synthesized mainly in the liver and to some extent in the small intestine. It plays an important role in cholesterol metabolism, along with HDL-C. The main function of HDL-C is to take up cholesterol in tissues and direct it back to the liver for excretion through the bile. One interesting observation mentioned by a meta-analysis of eight statin trials was that a rise in HDL after statin therapy had no significant cardiovascular benefit, whereas a rise in Apo A-1 resulted in a significant reduction of cardiovascular events. ApoA-I has the ability to reverse cholesterol transport (RCT), to bind lipids, and to activate lecithin cholesterol acyltransferase (LCAT) to form mature HDL.[12–15]

Apolipoprotein B exists in two forms, apo B-48 and apo B-100. Apo B-48 is synthesized in the intestine, where it is complexes with dietary triglycerides and free cholesterol absorbed from the gut lumen to form chylomicron particles. These are metabolized in the circulation and in the liver. Apo B-100 is synthesized in the liver and is present in Low Density Lipoprotein (LDL), Intermediate Density Lipoprotein (IDL) and Very Low Density Lipoprotein (VLDL) particles. Only one apo B molecule is present in each of these lipoprotein particles and therefore the total apo B value indicates the total number of potentially atherogenic lipoproteins. Apo B is essential for the binding of LDL particles to the LDL receptor, allowing cells to internalize LDL and thus absorb cholesterol. An excess of apo B containing particles is a main trigger in the atherogenic process. Small dense LDL particles are considered more atherogenic than large buoyant LDL molecules, as they are easily internalized into the subintimal space where they adhere to matrix proteoglycans, get oxidized and thereby increase the risk of atherothrombotic events.[16–18]

Atherosclerosis is considered an inflammatory process and hs-CRP an inflammatory marker is an independent predictor of future cardiovascular events. An increased level of hs-CRP has predictive value for future events in patients with diagnosed CAD and for development of disease in individuals with multiple risk factors for CAD. The CANTOS trial has proven that inflammation reduction in humans, at least by targeting IL-1β, significantly reduces vascular event rates in proportion to the magnitude of hs-CRP reduction achieved and in the absence of any effects on atherogenic lipids. The trial showed a statistically significant decrease in major adverse cardiac events (MACE) with Canakinumab which paralleled the reduction in hs-CRP.[19]

In the present study we compare levels of the various newer risk factors namely Lp-PLA2, Lp(a), apo(B), apo(A) and hs-CRP to the conventional risk factors for CAD namely diabetes, hypertension, dyslipidaemia and tobacco use.

2. Materials and Methods

2.1. Ethics

The proposal was cleared by the Institutional Ethics committee of XXX Institute of Medical sciences dated 16th February 2021, No: ECASM- AIMS-2021-127. Written informed consent was obtained from all the participants.

2.2. Study setting

Department of Cardiology, XXX Institute of Medical sciences (XXX).

2.3. Study design

Case control study design.

2.4. Study population

Cases: Cases are as any individual with coronary artery disease, defined as

1. History of an acute coronary syndrome, encompassing ST Elevation Myocardial Infarction (STEMI), Non-ST Elevation Myocardial Infarction (NSTEMI) and unstable angina as per the Fourth Universal definition of myocardial infarction.
2. History of revascularisation procedure for coronary artery disease (CAD) - either or both of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).
3. 50% stenosis of a major coronary artery on conventional or CT coronary angiogram.
4. Reversible ischaemia on exercise stress testing or dobutamine stress echo.

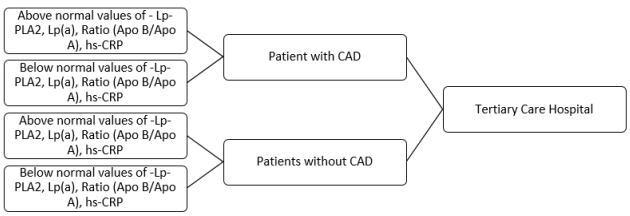

Fig. 1: Case control design

2.5. Controls

The controls included patients with non-coronary conditions including supraventricular tachycardia (SVT), valvular heart disease, atrial fibrillation, atypical chest pain with a normal epicardial coronaries or who presented as an outpatient for comprehensive health check-ups, with normal results for ischaemia but with one or more identified major risk factors for CVD; diabetes mellitus, hypertension, dyslipidaemia, tobacco use or a family history of CVD.

Non-consenting individuals, those aged > 80 years or < 18 years and pregnant women were excluded from the study.

2.6. Variables

Dependant variable- Coronary Artery Disease (CAD); Independent variables: Lp PLA2, Lp(a), Apo(a), Apo(b), Ratio (Apo B/Apo A); Other predictors- diabetes mellitus, hypertension, dyslipidaemia, tobacco use

2.7. Estimation of the markers

All biochemical analysis was done at Agappe diagnostics, on a Toshiba 120 FR automated analyser with exceptions to Lp(a), Apo(a), Apo(b) which were done on a MISPA 13 analyser. Blood was collected after 10 hours of overnight fasting in all subjects. The biochemical analysis used was, fasting plasma glucose (glucose oxidase method), lipid profile (CHOD-PAP method), Lp(a) (immunoturbidometric method), Lp-PLA2 (enzymatic method), apo A1, apo B (immunoturbidometric using nephelometry), hs-CRP (latex-based antibody coated reagent).

Majority of enrolled CAD patients were already on lipid lowering drugs for which a correction factor was applied to get the pre-statin LDL levels based on the drug prescribed. The correction factors were developed from the analysis of 71 original articles.[10] For 5, 10, 20, and 40 mg of rosuvastatin, the adjustment factor was 1.8, 1.9, 2.1, and 2.4, respectively. Similarly, for 10, 20, 40, and 80 mg of atorvastatin, the adjustment factor was 1.6, 1.8, 2.0, and 2.2, respectively, and, for 10 mg of ezetimibe, LDL-C adjustment factor was 1.2. Fibric acid derivatives were not corrected for. For example, adjusted cholesterol = actual measurement X cholesterol adjustment factor for medication/dose. The cut-off values used for the biochemical analysis were, Lp-PLA2 -35 mg%, Lp(a) -30mg%, Apo(b)-100mg%, Apo A1-180mg%, LDL- 100 mg% and hs-CRP- 2mg%.

In addition to markers following parameters were also assessed; anthropometric, laboratory parameters, medical conditions, socio-demographic and behavioural factors. Parameters entered included age, sex, body mass index (BMI), disease status vis a vis acute coronary syndrome (ACS), history of diabetes, dyslipidaemia or hypertension, family history of CVD, socio-behavioural habits including tobacco and alcohol use, exercise stress test report, LV function by ECHO, coronary angiogram report, SYNTAX score and revascularisation procedure-Percutaneous Coronary Intervention (PCI) /Coronary Artery

Table 1: Bivariate analysis of Coronary Artery disease with its risk factors

		Coronary Artery Disease					
		Yes		No		Total	P value
Variables		n	%	n	%	N	
Gender	Males	117	66.5	59	33.5		0.001
	Females	19	26.4	53	73.4		
Lp PLa2	≤ 35	133	56.4	103	43.6	236	0.032
	>35	3	25	9	75	12	
GFR	≥ 60	99	54.7	82	45.3	181	0.03
	< 59	26	52	24	48	50	
CRP	≤ 2	100	54.6	83	45.4	183	0.918
	> 2	36	55.4	29	44.6	65	
LDL	≤ 100	27	45	33	55	60	0.079
	> 100	109	58	79	42	188	
Lp(a)	> 30	85	50	85	50	170	0.024
	≤ 30	51	65.4	27	34.6	78	
Alcohol	Yes	13	65	7	35	20	0.341
	No	123	53.9	105	46.1	228	
Hypertension	Yes	110	64.7	60	35.3	170	
	No	26	33.3	52	66.7	78	
Dyslipidaemia	Yes	132	67.7	63	32.3	195	0.001
	No	4	7.5	49	92.5	53	
Apo(A)	<180	19	35.7	18	64.3	28	0.031
	≥180	126	57.3	94	42.7	220	
Apo(B)	≤100	123	59.7	83	40.3	206	0.001
	>100	13	31	29	69	42	
Ratio ApoB/ApoA	≤0.8	125	57.3	93	42.7	218	0.03
	>0.8	10	35.7	18	64.3	28	
Diabetes Mellitus Type 2	Presence	83	76.1	26	23.9	109	0.001
	Absence	53	38.1	86	61.9	139	
Blood Pressure	Presence	110	64.7	60	35.3	170	0.001
	Absence	26	33.3	52	66.7	78	
Age	>50	15	26.3	42	73.7	57	0.001
	≤50	121	63.7	69	36.3	190	
Tobacco	Presence	20	76.9	6	23.1	26	0.033
	Absence	116	52.3	106	47.7	222	

Bypass Graft (CABG).

2.8. Statistical analysis

We studied the independent association of the disease with age, sex, diabetes, hypertension, lipoprotein(a), Lp-PLA2, hs-CRP, apo A, apo B, lipids, tobacco and alcohol use. Categorical variables were presented as frequencies and percentages. Chi-square test was used to compare the categorical risk factors with the disease status. Binary logistic regression analysis was used to study the association of multiple factors on the disease status. All the analysis was performed using a SPSS version 20.0.

3. Results

A total of 253 participants; 140 cases and 113 controls were enrolled in this study. Table 1 shows the association of coronary artery disease with its risk factors. The participants were aged between 19 and 80 years with 63.7% of patients of CAD being less than 50 years of age. Except for the hs-CRP level, alcohol consumption and LDL, all the other risk factors were seen significantly associated with the coronary artery disease. Table 2 shows that among the CAD patients aged less than 50 years blood pressure, diabetes mellitus, Apo(b) and Apo B/Apo A ratio were significantly associated. In the multivariate analysis (Table 3), dyslipidaemia (10.8, 95% CI 3.29-35.37), male gender (4.68, 95% CI 2.12-10.30), diabetes mellitus (3.3, 95% CI 1.6 -6.77), lipoprotein(a) more than 30mg% (2.34,

Table 2: Bivariate analysis of age and other risk factors among coronary artery disease patients

		Age in years					
		less than 50		More than 50		Total	P value
Variables		n	%	n	%	N	
Gender	Males	11	9.4	106	90.6	117	0.133
	Females	4	21.1	15	78.9	19	
Lp PLa2	≤ 35	14	10.5	119	89.5	133	0.212
	>35	1	33.3	2	66.7	3	
GFR	≥ 60	10	10.1	89	89.9	99	0.446
	<59	4	15.4	22	84.6	26	
CRP	≤ 2	12	12	88	88	100	0.546
	> 2	3	8.3	33	91.7	36	
LDL	≤ 100	1	3.7	26	96.3	27	0.175
	>100	14	12.8	96	87.2	109	
Lp(a)	> 30	9	10.6	76	89.4	85	0.024
	≤ 30	6	11.8	45	88.2	51	
Alcohol	Yes	2	15.4	11	84.6	13	0.598
	No	13	10.6	110	89.4	123	
Dyslipidaemia	Yes	15	11.4	117	88.6	132	0.475
	No	0	0	4	100	4	
Apo(A)	<180	1	10	9	90	10	0.941
	≥180	14	11.1	121	136	126	
Apo(B)	≤100	11	8.9	112	91.1	123	0.038
	>100	4	30.8	9	69.2	13	
Ratio ApoB/ApoA	≤0.8	12	9.6	113	90.4	125	0.048
	>0.8	3	30	7	70	10	
Diabetes Mellitus Type 2	Presence	4	4.8	79	95.2	83	0.004
	Absence	11	20.8	42	79.5	53	
Blood Pressure	Presence	13	11.8	97	88.2	110	0.001
	Absence	2	7.7	24	92.3	26	
Tobacco	Absence	3	15	17	85	20	0.539
	Presence	12	10.3	104	89.7	116	

Table 3: Multivariate analysis association of CAD with risk factors

Variables		p-value	Odds ratio	95% C.I. for Odds Ratio	
				Lower	Upper
Presence of Diabetes	No	0.001	3.30	1.61	6.77
Presence of Hypertension	No	0.022	2.48	1.14	5.39
Presence of Dyslipidaemia	No	0.0001	10.80	3.29	35.37
Male	Female	0.0001	0.19	0.08	0.45
Lp(a) >30	Lp(a) ≤ 30	0.035	2.34	1.06	5.15
Lp-PLA2 > 35	Lp-PLA2 ≤ 35	0.662	1.73	0.14	20.65
Apo(a)<180	Apo(a)≥180	0.694	0.79	0.24	2.52
Apo(b) >100	Apo(b) ≤ 100	0.132	2.74	0.73	10.18
Ratio of Apo(b)/Apo(a) > 0.8	Ratio Apo(b)/Apo(a) ≤ 0.8	0.353	0.39	0.05	2.78
LDL > 100	LDL ≤ 100	0.102	0.48	0.20	1.15
CRP > 2	CRP ≤ 2	0.825	1.09	0.50	2.36
Age≤ 50 years	Age≥ 50 years	0.079	0.43	0.17	1.10

Dependent Variable Presence of Coronary Artery Disease

95% CI 1.06-5.15) and hypertension (2.48, 95% CI 1.14-5.39) had significant association with occurrence of CAD.

4. Discussion

That coronary artery disease cannot be ascribed to any single cause; is multi-factorial in causality and progression, results from a complex inter-play of social determinants, behavioural habits, lifestyle, genes and much described conventional risk factors is undisputed. What was previously considered a disease of high-income countries (HIC) is now more prevalent in low- and middle-income countries (LMICs) where exists 80% of the disease burden. CAD presents one to two decades earlier and in a more malignant and extensive pattern in Indians when compared with Western populations.

CAD has been extensively researched over the years and a number of unique markers have been studied, including homocysteine, apolipoprotein B, apolipoprotein A1, Lp-PLA2 (Lipoprotein associated phospholipase A2), intima media thickness (IMT), coronary calcium score, various lipid sub-fractions like small dense LDL, oxidised LDL, HDL fractions, Lp(a), oxidative stress markers like isoprostanes, malondialdehyde, myeloperoxidase etc, in spite of which a lot is still unknown about the disease process and its progression.

The present study compares on the risk factor profile between diagnosed cases of CAD versus controls, without CAD. The risk factors studied included behavioural, demographic, conventional risk factors, including diabetes, hypertension, dyslipidaemia and newer risk factors including Lp(a), hs-CRP, Lp-PLA2 and Apo B /Apo A ratio. Lp(a), Apo(B)/Apo(A) ratio, diabetes mellitus, systemic hypertension, dyslipidaemia showed a significant association with CAD both in the overall cohort of patients of CAD and in participants less than 50 years of age with CAD. Multivariate analysis of the association between CAD and risk factors revealed a significant association between diabetes, hypertension, dyslipidaemia, Lp(a)and gender. The association of Lp-PLA2, hs-CRP and Apo (B)/ Apo (A) with CAD did not acquire statistical significance.

The limitations of the study include in that all the cases (patients of CAD) were on treatment for the same which could have modified the biochemical risk factors namely Apo(B), Apo (A), Lp(a) and Lp-PLA2 to some extent and also in the fact that duration of treatment for CAD has not been factored for. Another limitation of the study is in that the treatment aspects have not been analysed and the effect of the four mandated drugs for the treatment of CAD namely beta blockers, angiotensin converting enzyme receptor inhibitors (ACEI), statins and anti-platelet drugs have not been factored for.

We assessed the severity and extent of CAD from the SYNTAX score 23 and above as a cut-off for extensive disease. The same did not reach statistical significance as the majority of patients had a score < 22 with only 7 of the 146 cases having a score of > 22.

The results of the analysis from a single tertiary care centre are not a representative sample and the results could be generalised to the country or region.

5. Conclusion

From among the biochemical risk factors for CAD namely Lp(a), Apo (A1), Apo (B) and Lp-PLA2 only Lp(a) showed statistical significance in its association with CAD. Lp-PLA2, Apo(A1) and Apo(B) and its ratio showed a small degree of association not reaching statistical significance. The conventional risk factors namely hypertension, diabetes and dyslipidaemia showed a significant strength of association with CAD. Analysis of risk factor profile in participants with CAD (cases) less than the age of 50 showed statistical significant degree of association with the conventional risk factors and Lp(a) while not reaching significance with Lp-PLA2, Apo(A1) and Apo(B). Larger studies comparing the conventional to the biochemical risk factors are necessary in order to prove the trends shown with the strength of association. Individuals with CAD with none of the conventional risk factors need be tested with these biochemical markers of CAD especially Lp(a) especially with premature coronary artery disease.

6. Clinical perspective

Inflammation has been recognised as one of the main drivers of atherosclerosis. Different markers of inflammation have been identified and studied over the years of which hs-CRP has been the most studied with numerous clinical trials testifying its efficacy in risk stratification for CAD, as a prognosticator in those with disease as also the effectiveness of therapy. Lp-PLA2 has been less studied as compared to hs-CRP with trials done in Western countries suggesting its role as a marker for CAD.

In the present study we analyse the role of inflammatory mediators of CAD (hs-CRP, Lp-PLA2), pro-thrombotic markers [Lp(a)] and lipid fractions apoB, apo A and their ratio to assess which of these biochemical markers predisposed one to CAD through assessment of the relative risk.

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8. Conflicting Interest

All the authors have declared that there has been no conflict of interest at any stage of the study.

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Author biography

Rajesh Thachathodiyil, Head

Anugrah Nair, Senior Resident

Rajiv Chandrasekhar, Professor

Natarajan Kumaraswamy, Professor

Vijayakumar Maniyal, Additional Professor

Praveen G Pai, Additional Professor

Navine Mathew, Additional Professor

Harikrishnan S Madhavankutty, Additional Professor

Saritha Sekhar, Associate-Professor

Hisham Ahmed, Associate Professor

Jofy Paul, AVP

Riji Thomas, Senior Research Officer

Aneesa Ayoob, Senior Resident

Chandrasekhar Janakiram, Professor

Jaideep C Menon, Consultant Cardiologist https://orcid.org/0000-0002-0786-8123

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