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Original Research Article

Correlation of Lipoprotein Phospholipase A2 (Lppla2) Levels With Severity of Coronary Artery Disease: An Observational Study

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Abstract

Background: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a predictor biomarker for incident atherosclerotic disease. Lp-PLA2 has been recognized in atherosclerotic plaques; however, its role in atherosclerosis is still a matter of exploration. Lp-PLA2 belongs to the superfamily of phospholipase A2 enzymes. It is produced by macrophage that appears to play a role in the atherosclerotic vessel wall. Evolving data appear to suggest that Lp-PLA2 may be pro-atherogenic, which is thought to be mediated by lypo-phosphatidylcholine and oxidized non-esterified fatty acids, two mediators generated by Lp-PLA2. Phospholipase A2 plays an essential role in metabolism of membrane phospholipids, it is related to inflammatory reactions, secretion of amyloid precursor protein. Several studies have documented association of Lp-PLA2 with coronary heart disease in the general population. The present original research article focuses particularly on whether LP-PLA2 activity is positively associated with the severity of Coronary artery disease (CAD).

Methods: It was a prospective observational study where fifty consecutive proven cases of coronary artery disease and 50 consecutive cases with normal coronary angiography were enrolled in the study. We classified the cases as mild moderate and severe according to SYNTAX score. There were 19 cases of Mild CAD, 18 and 13 cases belonged to moderate and severe disease respectively. LpPLA2 mass levels were measured for all controls and cases. at LpPLA2 levels correlate significantly with LDL levels.

Results: Analysis of data failed to establish any correlation between LpPLA2 and Severity of CAD. Rather we found the LpPLA2 levels correlate with LDL levels. Levels of LpPLA2 also show reduction after statin treatment along with LDL levels. LpPLA2 levels do not correlate with severity of CAD especially in patients on statin treatment.

Recommendation and conclusion: Based on our study we can recommend that LpPLA2 level may not be measured to assess severity of Coronary artery disease especially in patients on statin treatment.

Keywords: Lipoprotein-Associated Phospholipase A2 (Lppla2), Cardiovascular Disease, Coronary Artery Diseases, Coronary Angiography.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is still the leading cause of morbidity and mortality worldwide **[1]** despite great advances on diagnosis and treatments have been achieved in the past decades. Inflammation plays critical and continuous roles on the initiation and progression of atherosclerosis and ASCVD, and increased serum level of inflammatory biomarker such as high sensitivity C-reactive protein (hs-CRP) has been recognized as an important predictor for cardiovascular diseases risk **[2]**. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is an enzyme excreting predominantly from atherosclerotic plaques by macrophages and neutrophils and then circulating in blood stream. Previous clinical epidemiological studies showed that increased plasma level of Lp-PLA2 was associated with increased risk of cardiovascular events such as myocardial infarction and ischemic stroke.

LpPLA2 has been proven as an independent prognostic factor in Coronary Artery Disease. Previous western and Chinese studies suggest that LpPLA2 is an indicator of severity of coronary artery disease and levels were found to be higher in patients with multivessel disease. Patients with acute coronary syndrome also had higher LpPLA2 level as compared to stable angina, suggesting its role as a marker of plaque vulnerability.

The US Food and Drug Administration (FDA) has approved a screening test that measures serum lipoprotein-associated phospholipase A2 (Lp-PLA2) for the assessment of coronary heart disease (CHD) risk in patients without existing disease [(3)]. Our study aims to study the level of LpPLA2 and its co-relation with severity of CAD in Indian population.

Material and Methods

Study site: Department of Cardiology and Department of Laboratory Medicine, in a tertiary care hospital**.**

Study Population: Patients of all age groups and both gender who have undergone coronary angiography at our centre were studied.

50 consecutive patients with proven CAD by angiography (>/= 50% coronary artery stenosis) were enrolled as cases.

50 consecutive cases of </= 50% coronary artery stenosis. (Normal coronary angiographies) were enrolled as controls.

Study Design: Prospective observational study

Sample size: 100, Cases: 50, Controls: 50

Inclusion criteria

Patients of all age groups and both genders undergoing CAG as a part of evaluation for angina at Dept. of Cardiology were eligible.

Exclusion criteria

1. Patients not fit for CAG
2. Patients with Acute Coronary syndrome (Unstable Angina/ NSTEMI and STEMI)

Methods

Cases and controls were enrolled at cardiac catherization lab (Cathlab) at Dept. of Cardiology Patients who were scheduled for coronary angiography as parts of

evaluation for stable angina were considered. After CAG, they were divided into Cases and Controls as per criteria mentioned below.

We enrolled 50 consecutive patients who were proven to have coronary artery disease by angiography. Coronary Artery Disease (CAD) was defined as >50% stenosis in any coronary artery of more than 1.5mm caliber after obtaining informed consent.

50 consecutive subjects who did not fulfill the above angiography criteria for coronary artery disease were enrolled as controls after obtaining their informed consent.

Clinical history was recorded at the time of enrollment and old medical records were scanned for risk factors of ASCVD. The following parameters were evaluated:

1. **Age:** Risk of CAD increases after 45 years in Males and 55 years in females.
2. Sex Females in the child bearing age group are at low risk of CAD thanks to the protective effects of estrogen. Male sex is a risk factor for CAD.
3. **Family history:** Positive family history of premature CAD gives a cumulative risk afforded by genetic and common environmental factors. Thus history of CAD and or sudden cardiac death in a blood relative before the age of 45 years in Male and 55 years in females was considered positive family history.
4. **Diabetes Mellitus:** Patients with history of diabetes mellitus and treatment with oral hypoglycemic agents and or insulin or HbA1c >6.5 or Fasting blood glucose >126mg/dl were labelled Diabetic.
5. **Hypertension:** History of hypertension and or treatment for same or BP > 140/90 was considered positive risk factor.
6. Obesity BMI >25 kg/m2 was labelled obese.
7. Sedentary lifestyle Patients involved in desk jobs and who did not participate in sports or did not exercise regularly were considered to have sedentary lifestyle
8. Smoking Any amount of current smoking was considered risk factor.
9. Dyslipidemia

For patients with no risk factors for CAD
Total cholesterol >200mg/dl
LDL C >130mg/dl HDL-C <40md/dl
Triglycerides >150mg/dl
For patients with risk factors of CAD LDL-C >100
Patients with diagnosed CAD LDL-C>70
Or history of statin treatment was considered as surrogate for dyslipidemia

10. **Chronic Kidney disease:** S. creatinine >1.2 in absence of any acute cause was considered as risk factor.
11. Peripheral Vascular disease History of intermittent claudication was a risk factor.
12. Cerebrovascular accident Stroke is considered a risk factor.

The Blood sampling was be done before angiography and LpPLA2 level test was run on this sample.

After CAG, patient having normal coronary arteries or those with coronary arterial stenosis <50% in any vessel more than 1.5mm caliber were labeled as control. Patients with ≥50% stenosis in any vessel ≥1.5 mm caliber will be labeled to have CAD and classified according to SYNTAX score. The SYNTAX score reflects a comprehensive anatomical assessment, with higher scores indicating more complex coronary disease; a low score was defined as ≤22, an intermediate score as 23 to 32, and a high score as ≥33. Online SYNTAX score calculator was used for this purpose. (http://ir-nwr.ru/calculators/syntaxscore/frameset.htm)

Observation and Results

The study was carried out at Department of Cardiology, at a tertiary care centre in Mumbai . Fifty consecutive proven cases of coronary artery disease and 50 consecutive cases with normal coronary angiography were enrolled in the study.

Baseline Population Characteristics

Age distribution

Mean age of controls was 55.86 (SD 8.26) years. Youngest control was 40 year old and eldest 73 years old. Mean age of cases was 60.68 (SD 9.77) years. Minimum age was 44 and maximum 86. Controls were younger than cases (p=0.02)

Table 1: Age distribution

Age group (years)	Cases		Controls	
	Male	Female	Male	Female
40-50	7	1	9	6
50-60	15	3	11	7
60-70	10	4	8	5
70-80	6	3	2	2
80-90	1	0	0	0
Total	39	11	30	20

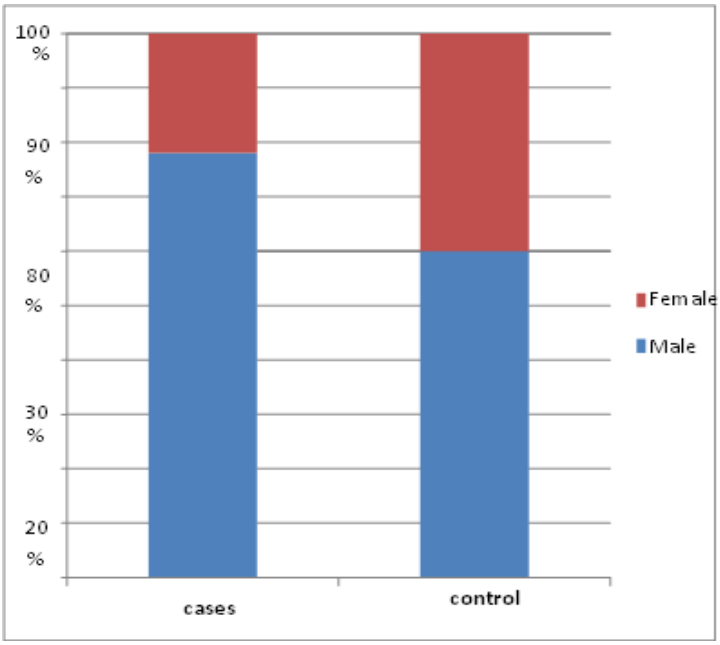

Figure 1: Sex distribution

Figure no 1 shows the sex distribution amongst cases and control. There were 11 female patients and 39 male patients. Amongst controls females were 20 and males were 30.

Risk Factors for Coronary Artery Disease

Presence of irreversible risk factors namely; age, sex, and family history and reversible risk factors; Diabetes Mellitus, hypertension, dyslipidemia, obesity, Chronic kidney disease, smoking and sedentary lifestyle were recorded in cases and controls by questionnaire and scanning of old medical records (Fig no 2)

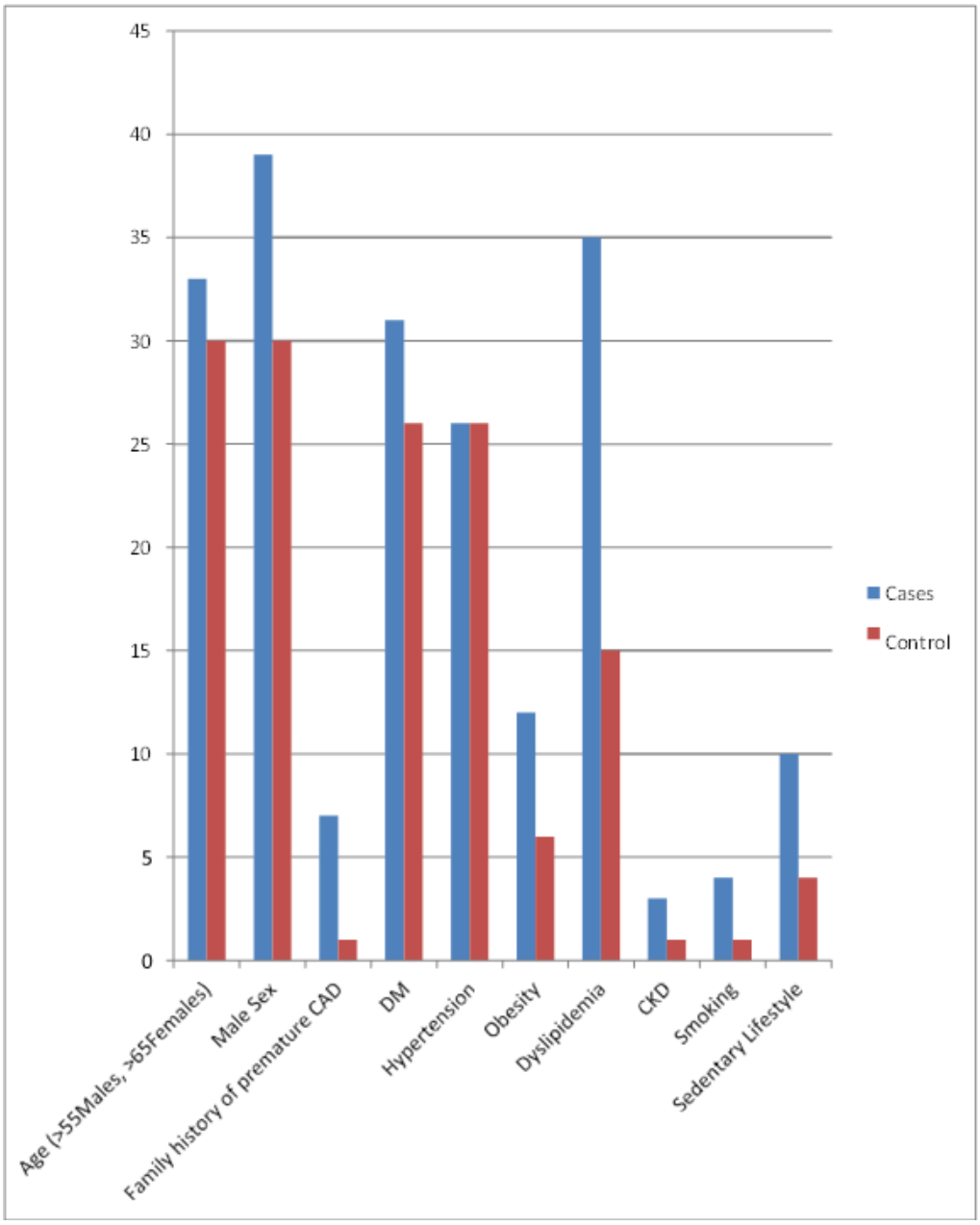

Figure 2: Distribution of risk factors

None of the cases or controls had been previously diagnosed with Peripheral vascular disease (PVD) or Cerebrovascular accident (CVA).

Table 2: Distribution of risk factors

Risk Factor	Cases	Control	P value
Age (>45Males, >55Females)	46	38	0.056
Male Sex	39	30	0.08
Familyhistory of premature CAD	7	1	0.06
DM	31	26	0.4
Hypertension	26	26	1
Obesity	12	6	0.4
Dyslipidemia/ on statin	48	30	<0.001
LDL levels	Mean =101 (SD=40)	Mean=95(SD=31)	0.42

CKD	3	1	0.6
Smoking	4	1	0.3
Sedentary Lifestyle	10	4	0.14

Two cases and one control were on treatment for Hypothyroidism. One control was a old treated case of Ca Breast. One male patient had Obstructive sleep apnoea. Risk factors were evenly distributed among cases and controls except dyslipidemia which had higher incidence in the CAD group (48 vs 30, p value 0.001). This difference was statistically significant.

Lipid levels

Dyslipidemia was determined based on previous medical records and not according to latest lipid profile. 48 cases were labelled as dyslipidemia or were on statin treatment at the time of enrollment. Range of Total Cholesterol was 66 to 276 mg/dl (Mean 164, SD 49, 95%CI 149 to 178) Mean LDL (Low Density Lipoprotein) amongst cases was 101mg/dl (SD 40, 95% CI 89- 112) Only 15 cases had achieved LDL level less than 70mg/dl. 8 cases had LDL levels between 70-100mg/dl. Rest of the 33 cases had LDL levels above 100mg/dl. Mean HDL (High Density Lipoprotein) levels were 38mg/dl (SD 38, 95% CI 36-41). Serum Triglycerides (TG) levels varied from 43 to 357 mg/dl, mean levels being 124mg/dl (SD 64, 95%CI 106 to 142) .

In the control group 30 patients were diagnosed to have dyslipidemia and were on statin treatment at the time of enrollment as per old medical records. Total Cholesterol was in the range of 101 to 268mg/dl with a mean of 160 (SD 37, 95%CI 150 to 168). Minimum LDL levels were 35 to 205mg/dl, mean 95mg/dl (SD 32, 95%CI 86 to 104). HDL level range amongst controls was 24 -60 mg/dl (mean 40, SD 10, 95%CI 37to 43). TG levels were in the range 43 to 225 mg/dl (mean 113, SD 50, 95%CI 98 to 127).

Table no. 5 and figure no. 6 show comparison of LDL levels between the two groups. The cases group had relatively high no. of patients who had higher LDL levels than desired. 33 (66%) cases had LDL more than 100mg/dl. Desired levels of LDL in secondary prevention are less than 70mg/dl, only 15 cases (30%) had achieved that goal.

Most cholesterol is normally carried in LDL-C. Over a wide range of plasma cholesterol concentrations, there is a strong and graded positive association between total as well as LDL-C and risk of CVD. This association applies to men and women, and to those without CVD as well as with established CVD. The evidence that reducing plasma LDL-C reduces CVD risk is unequivocal; the results of epidemiological studies and trials with and without statins using angiographic or clinical endpoints confirm that the reduction of LDL-C is of prime concern in the prevention of CVD.

Table 3: Comparison of LDL levels between cases and control population

LDL level (mg/dl)	Cases	Control
<70	15	15
70-100	8	16
>100	33	19

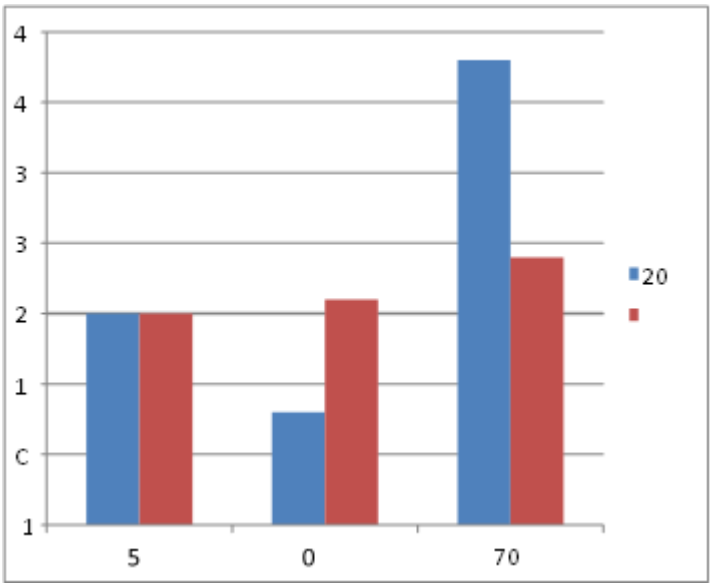

Figure 3: Comparison of LDL level.

Low HDL-C is independently associated with higher CVD risk. Desired level of HDL is >40mg/dl. 28 cases and 26 controls had HDL >40mg/dl. Table no 4 and figure no 4 show comparison of HDL level amongst both groups (see table no 4 and figure no 4)

Table 4: Comparison of HDL levels between cases and controls

HDL levels (mg/dl)	Cases	Controls
<40	22	24
>40	28	26

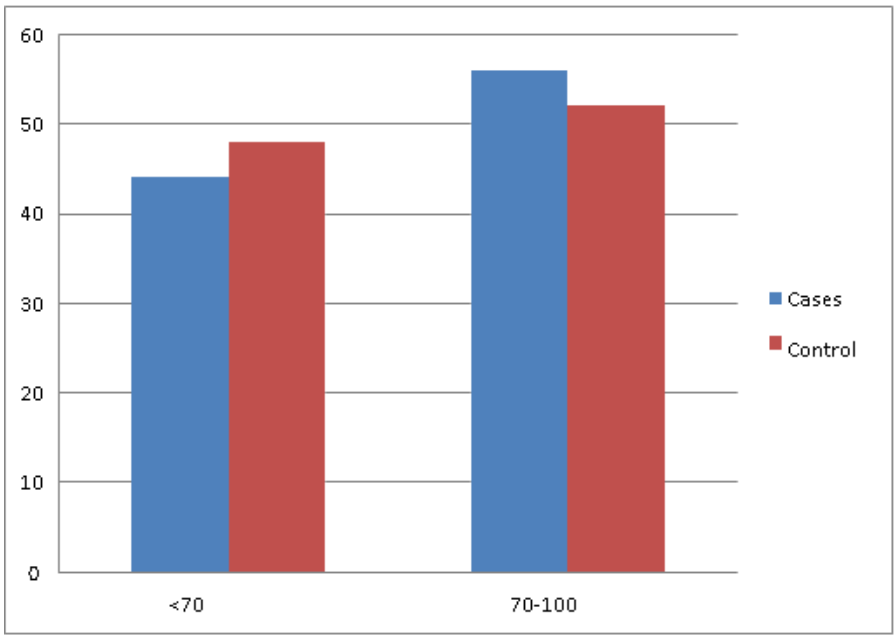

Figure 4: Comparison of HDL levels between cases and control

Hypertriglyceridemia is a significant independent CVD risk factor, but the association is far weaker than for hypercholesterolemia. The risk is associated more strongly with moderate than with very severe hypertriglyceridemia (900 mg/dL) which is a risk factor for pancreatitis. There are, however, no randomized trials to provide sufficient evidence to derive target levels for

triglycerides. Meta-analyses suggest that targeting triglycerides may reduce CVD in specific subgroups with high triglycerides and low HDL-C. At present, fasting triglycerides < 150 mg/dL continue to be considered a marker of increased risk. Table no 7 and Figure no 8 show proportion of cases and controls with triglyceride levels <150mg/dl.

Table 5: Comparison of Triglyceride levels between cases and controls

Triglyceride level (mg/dl)	Cases	Control
<150	37	36
>150	13	14

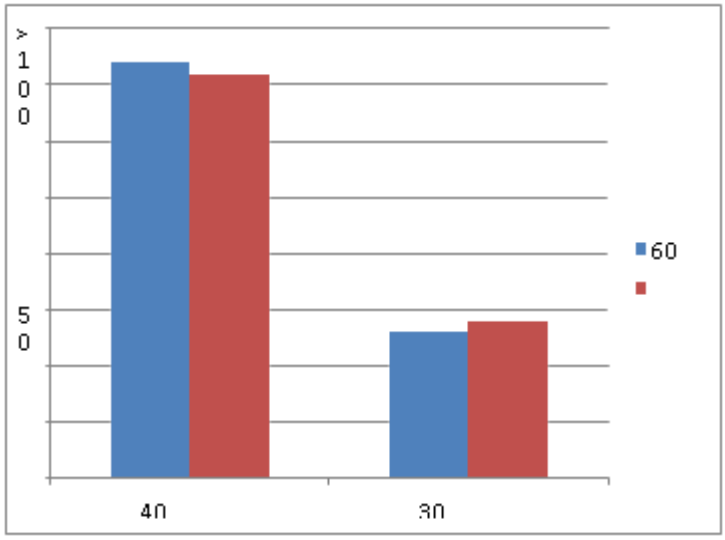

Figure 5: Comparison of TG levels between cases and controls.

Classification of cases according to severity of CAD.

After coronary angiography, at the time of enrollment patients were grouped as cases and controls on the basis of presence of coronary artery disease (>50% stenosis in any artery >1.5mm diameter). Cases were further classified into three groups; mild, moderate and severe by SYNTAX score. See table no 6 and figure no 6.

Table 6: Classification of cases as per severity of CAD.

SYNTAX score	No of case
<22 – Mild disease	19
22-33- Moderate disease	18
>33- Severe disease	13

Minimum value obtained was 1 which was seen in a 68 year old female patient with focal non calcific 80% proximal RCA stenosis which indicates a mild disease. The most severe form of CAD was seen in a 61-year male patient with severe triple vessel disease and severe LV dysfunction whose SYNTAX score was 57. Mean SYNTAX score was found to be 22 (SD= 14).

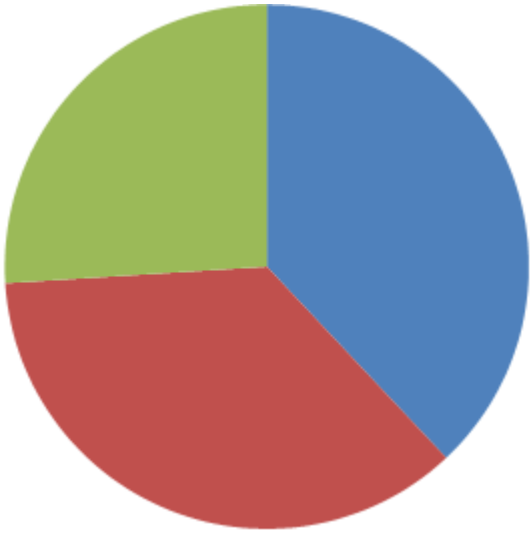

Figure 6: Distribution of Severity of Coronary artery disease.

LpPLA2 (Lipoprotein phospholipase A2) mass levels were estimated in all the cases and controls. We compared LpPLA2 mass levels across all severity groups of CAD and controls and studied its correlation with SYNTAX score.

LpPLA2 mass levels were recorded (See Table no 7). Comparison between mean LpPLA2 levels amongst the groups does not show any correlation with severity of the disease. Mean value of LpPLA2 in control group [109ng/ml (SD=49)] was more than that in the group of severe CAD [88ng/ml (SD=50)].

Table 7: LpPLA2 levels across spectrum of CAD

	N	Mean	Std. Deviation	Std. Error
Control	50	109.5524	43.98254	6.22007
Mild	19	95.5021	44.22602	10.14614
Moderate	18	118.5467	45.38488	10.69732
Severe	13	88.2815	50.21510	13.92716
Total	100	105.7366	45.49431	4.54943

Table 8: ANOVA test to determine significance LpPLA2 between the groups

	Df	F	Sig.
Between Groups	3	1.579	0.200

LpPLA2 levels were normally distributed in all groups (Shapiro Wilk test). One way ANOVA with post hoc Tuckey's test was applied for multiple comparisons. There was no significant difference in LpPLA2 levels between groups.

Table 9: Tukey test showing no significant difference of LpPLA2 levels between the groups.

(I) Groups	(J) Groups	Sig.	95% Confidence Interval	
			Lower Bound	Upper Bound
Control	Mild	0.656	-17.7296	45.8302
	Moderate	0.887	-41.4075	23.4190
	Severe	0.433	-15.4407	57.9824
Mild	Control	0.656	-45.8302	17.7296
	Moderate	0.410	-61.8308	15.7416

	Severe	0.970	-35.2234	49.6645
Moderate	Control	0.887	-23.4190	41.4075
	Mild	0.410	-15.7416	61.8308
	Severe	0.260	-12.6551	73.1854
Severe	Control	0.433	-57.9824	15.4407
	Mild	0.970	-49.6645	35.2234
	Moderate	0.260	-73.1854	12.6551

LpPLA2 vs SYNTAX score

We studied the correlation of LpPLA2 mass level with SYNTAX score. (See figure no 7)

A Spearman's rank-order correlation was run to determine the relationship between LpPLA2 and Syntax score. There was very weak negative correlation between LpPLA2 and Syntax score, which was statistically not significant (r_s = -.101, p = .485; table no 9). This means LpPLA2 levels do not reflect severity of CAD.

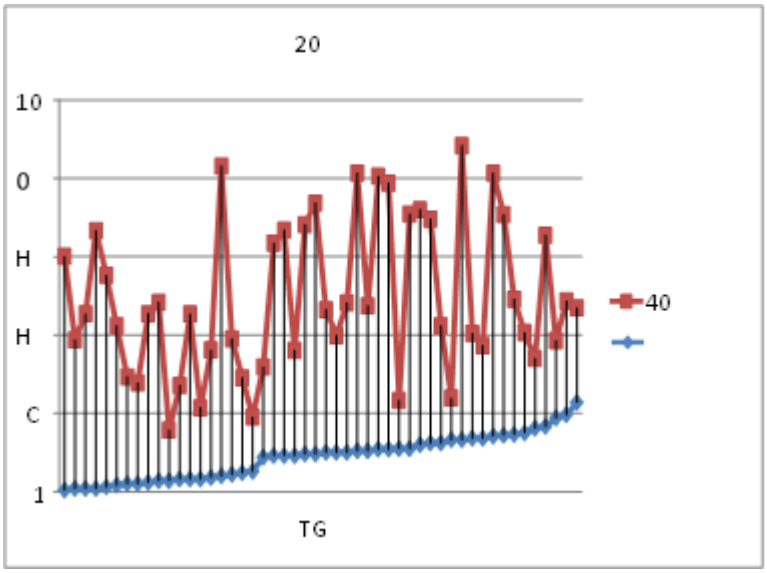

Figure 7: SYNTAX SCORE vs. LpPLA2 levels

Table 9: Correlation between Syntax score and LpPLA2

			Syntax	**LpPLA2**
Spearman's rho	Syntax	Correlation Coefficient	1.000	-0.101
		Sig. (2-tailed)		0.485
		N	50	50
	LpPLA2	Correlation Coefficient	-0.101	1.000
		Sig. (2-tailed)	0.485	
		N	50	50

LpPLA2 levels vs LDL levels

Circulating LpPLA2 is bound to LDL cholesterol. Thus any factor that affects LDL level to drop will cause reduction in LpPLA2 levels. In our study 96% cases and 60% controls were on Statin treatment. Statins reduce LpPLA2 levels. This is achieved by

Statins reduce LDL level, thereby reducing circulating LpPLA2 bound to LDL.

Statins also reduce vascular inflammation (evident by its ability to reduce hs CRP) thereby reducing production of LpPLA2.

Observation of LDL and LpPLA2 levels in our study also reflects that they are correlated. In JUPITER trial sub analysis it was found that levels of Lp-PLA2 mass and activity correlated moderately with each other and with LDL-C. The magnitude of these correlations increased after statin therapy. Rosuvastatin reduced Lp-PLA2 mass by 33.8%, Lp-PLA2 activity by 33.2%, and LDL-C by 48.7% (p 0.0001).

We studied correlation of LpPLA2 levels with LDL. A Spearman's rank-order correlation was run to determine the relationship between LpPLA2 and LDL levels. There was moderate positive correlation between LpPLA2 and LDL levels, which was statistically significant (r_s = .401, p =.004, see table no 10 and figure no 8).

Table 10 : Correlation of LpPLA2 level with LDL level

			LpPLA2	LDL
Spearman's rho	LpPLA2	Correlation Coefficient	1.000	0.401
		Sig. (2-tailed)		0.004
		N	50	50
	LDL	Correlation Coefficient	0.401	1.000
		Sig. (2-tailed)	0.004	
		N	50	50

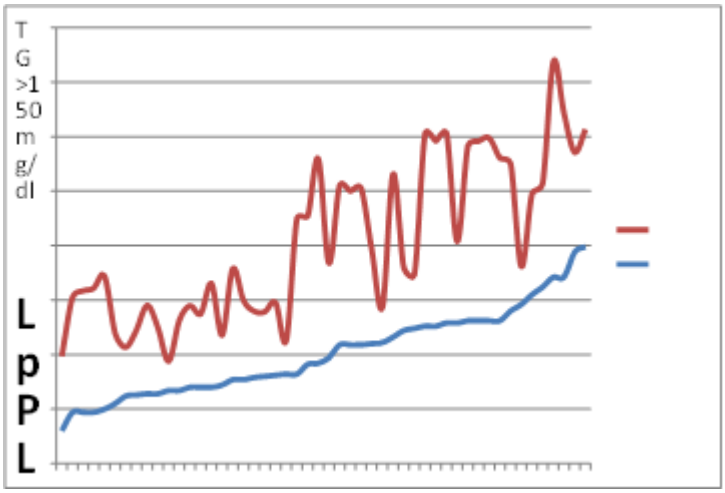

Figure 8: Correlation of LDL and LpPLA2 levels

Thus after analysis of the data from this study we can draw following conclusions:

1. Plasma LpPLA2 levels correlate with LDL levels (r_s = .401, p = .004)
2. Statin treatment reduces LpPLA2 levels.
3. Plasma LpPLA2 levels do not correlate with severity of coronary artery disease in patients of Stable angina.

Whether residual risk for CAD can be determined from LpPLA2 level cannot be determined from this study.

Discussion

This study intended to probe the relationship between Lipoprotein phospholipase A2 and severity of coronary artery disease. We studied 50 cases of stable coronary artery disease, defined as more than 50% stenosis in a coronary artery more than 1.5mm in caliber and 50 such patients who did not meet the angiography criteria as controls.

Coronary artery disease has heterogeneous risk factors. Traditional risk factors of CAD were evaluated among cases and controls.

The risk of coronary artery disease increases with age. Males >45 years and Females >55years have incremental risk for ASCVD. Young females in their reproductive age group have lesser CAD risk owing to the protective effect of estrogen. In our study 46 (92%) cases and 38 (76%) controls were above this age. Males were 39 (78%) in CAD group and 30(60%) in the control group.

Familial history of premature CVD is a crude but simple indicator of the risk of developing CVD, reflecting both the genetic trait and the environment shared among household members. A positive family history of premature CV death is associated with an increased risk of early and lifetime CVD. A family history of premature CVD is simple, inexpensive information that should be part of the CV risk assessment in all subjects. Seven patients in the CAD group had positive family history against only one patient in the control group. The difference was not statistically significant though. [3]

The INTERHEART case control study [4] evaluated the effects of potentially modifiable risk factors associated with myocardial infarction across 52 countries. This study included 15152 cases and 14820 controls. They established Odd's ratio (OR) and Population attributable risks (PAR) for these risk factors (see table no 11).

Table 11: Results of INTERHEART study

Risk factor	OR	PAR (%)
Diabetes Mellitus	2.37	9.9
Hypertension	1.91	17.9
Smoking	2.87	35.7
Raised Apo B/ Apo A1	3.25	49.2
Central Obesity	1.12	20.1
Psychosocial factors	2.67	32.5
Consumption of fruits and vegetables	0.7	13.7
Consumption of Alcohol	0.91	6.7
Regular exercise	0.86	12.2

They concluded Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity account for most of the risk of myocardial infarction worldwide in both sexes and at all ages in all regions. This finding suggests that approaches to prevention can be based on similar principles worldwide and have the potential to prevent most premature cases of myocardial infarction.

Our study in contrast was done on the patients of stable coronary artery disease. Though the risk factors for atherosclerosis remain same and stable angina and myocardial infarction are different manifestation of the same disease spectrum. In our study the risk factors were evenly distributed amongst cases and control. This observation could be attributed to the fact that,

1. Our sample size was small, and
2. There was a selection bias of controls as they were also patients being evaluated for chest pain and shared risk factors of CAD. They underwent coronary angiography to rule out CAD.

We classified the cases as mild moderate and severe according to SYNTAX score [5]. There were 19 cases of Mild CAD, 18 and 13 cases belonged to moderate and severe disease respectively. LpPLA2 mass levels were measured for all controls and cases. Analysis of data failed to establish any correlation between LpPLA2 and Severity of CAD(r_s = -.101, p = .485). Rather we found that LpPLA2 levels

correlate significantly with LDL levels (r_s = .401, p = .004).

At first glance, the fact that levels of Lp-PLA2 mass in our study did not predict severity of CAD may seem surprising because positive effects were reported for prior studies. For example, in a collaborative analysis of 32 prior prospective studies, each SD increase in Lp-PLA2 mass was associated with an increase in relative risk of 1.11 for coronary heart disease (95% CI 1.07– 1.24) [6] . On the other hand, in that meta-analysis, not all prior studies were positive, nor did all assays used for the measurement of Lp-PLA2 mass perform similarly. Furthermore, because substantial variation in measured levels was observed between studies, the meta-analysis required the use of normalized LpPLA2 values that, although biologically informative, greatly limit clinical application. These data highlight the complexity of using Lp-PLA2 mass in clinical practice. Commercial algorithms for the use of LpPLA2 mass indicate that patient values above or below200 g/L have clinical relevance for risk prediction. The finding of wide variation of median levels for Lp-PLA2 mass across many populations presents a substantive calibration issue that could further limit the use of LpPLA2. Normal values for Indian population have not been established

Paul Ridker et al [7] analyzed the data generated in the JUPITER trial (Justification for the Use of Stat ins in Prevention: an Intervention Trial Evaluating Rosuvastatin) to evaluate the relationship of Lipoprotein-Associated Phospholipase a2 mass and activity with incident vascular events among primary prevention patients allocated to placebo or to statin therapy. They evaluated Lp- PLA2 mass concentration and activity were evaluated at baseline and after treatment in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial comparing rosuvastatin 20 mg to placebo among 17 802 men and women without cardiovascular disease or diabetes at study entry. The relationships of LpPLA 2 mass and activity with risk of future vascular events were evaluated in the placebo and rosuvastatin groups.

The results were

1. Among those study participants allocated to placebo, increasing quartiles of Lp-PLA2 activity (*P*trend 0.04) but not Lp-PLA2 mass (*P*trend 0.92) were associated with incident cardiovascular events after adjustment for LDL-C and conventional risk factors. Lp-PLA2 is physically linked to LDL cholesterol (LDL-C).
2. Before randomization, levels of Lp-PLA2 mass and activity correlated moderately with each other and with LDL-C.
3. The magnitude of these correlations increased after statin therapy. Rosuvastatin reduced Lp-PLA2 mass by 33.8%, Lp-PLA2 activity by 33.2%, and LDL-C by 48.7% (all *P* 0.0001). Comparable analyses conducted among those allocated to rosuvastatin revealed no significant relationship between LpPLA2 levels and subsequent vascular events. The ability of rosuvastatin to reduce vascular events was not significantly modified by baseline Lp-PLA2 level.
4. However, Lp-PLA2 no longer predicted risk or modified clinical outcomes when participants were treated with rosuvastatin.

In our study 48 patients in CAD group and 30 patients were on statin treatment. In these patient LpPLA2 levels were low irrespective of their severity of disease (SYNTAX score). Rather we found that LDL levels correlate with LpPLA2 levels (r_s = .401, p = .004).

Angping Cai et al [8] conducted a study to investigate whether increased plasma Lp-PLA2 level is independently associated

with the severity of coronary artery diseases. 781 participants were enrolled and coronary angiography (CAG) was performed. According to clinical presentation, electrocardiography, cardiac biomarker, and CAG result, participants were divided into control (excluded CAD), stable angina (SA), unstable angina (UA) and acute myocardial infarction (AMI) groups. Baseline characteristics were recorded. Statistical analyses were performed to evaluate the relationship between Lp-PLA2 level and CAD severity. The Results were as follows:

1. Plasma levels of Lp-PLA2 in control, SA, UA and AMI groups were 7.38(3.33-9.26) μg/L, 5.94(2.89-8.55) μg/L, 8.56(5.34-11.95) μg/L and 8.68(5.56-13.27) μg/L respectively ($P < 0.001$).
1. After adjusted for age, gender, smoking, diabetes mellitus, hypertension, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), apoprotein A (apoA) and statins, Lp-PLA2 level was still independently associated with CAD severity, with odd ratio (OR) of 1.055 (AMI group versus control group, 95% confidence interval (CI) 1.021-1.090, $P < 0.05$).
2. The relationship between Lp-PLA2 level and the number of stenosis coronary artery was also assessed. Lp-PLA2 levels in control, single-vessel, and multiple-vessels stenosis groups were 7.38(3.33-9.26) μg/L, 7.80 (4.05-10.76) μg/L and 8.29(5.18-11.76) μg/L respectively (P for trend < 0.001).
3. After adjusted for age, gender, smoking, diabetes mellitus, hypertension, LDL-C and HDL-C, apoA and statins, Lp-PLA2 level remained independently associated with the number of coronary artery stenosis, with OR of 1.053 (multiple-vessels stenosis group versus control group, 95% CI 1.025-1.069, $P < 0.05$).

They concluded that increased Lp-PLA2 level is independently associated with CAD severity, and Lp-PLA2 level may be used to discriminate those who are at increased risk of cardiovascular events.

Results of our study are in contrast with findings of above study. Our study did not show any significant correlation between LpPLA2 and severity of CAD. The reason of this difference could be due to

1. We excluded patients of myocardial infarction from our study. PROVE-IT TIMI 22(The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) did not show utility of measuring Lp-PLA2 in patients at the time of ACS, Lp-PLA2 measured 30 days post-ACS predicted future recurrent events with HR of 1.33(95%CI1.01–1.74) . This data would suggest that Lp-PLA2 is not a marker of acute coronary events but may rather reflect an increased risk of progression to coronary instability. Thus, patients of AMI in study by Angping Cai et al recorded higher LpPLA2 levels. Measuring LpPLA2 levels at the time of AMI may not add to the prognosis.
2. Angping et al classified CAD as Control, Single Vessel Disease and Multivessel disease and compared LpPLA2 levels amongst them. We classified severity of CAD according to SYNTAX score which is a more refined method.

Rathore et al [9] studied 150 normal healthy individuals (105 were males and 45 were females) and 150 CAD patients (122 were males and 28 were females) to assess lipoprotein-associated phospholipase a2 in coronary artery disease patients of North India. The study revealed that

1. Lp-PLA2 levels in normal healthy individual were 28.50ng/ml(±5.41) and 31.72ng/ml(±6.83) for male and female, respectively.. The Lp-PLA2

levels ranged between 17.12 to 32.43 ng/ml in males and 19.21 to 36.68 ng/ml.

2. Among CAD patients, 81.33% were males and 18.66% were females. Lp-PLA2 levels in CAD patients were 39.34±10.37 and 43.22±7.62 ng/ml for males and females respectively. The range of Lp-PLA2 in male patients was 26.38 to 50.16 ng/ml and 33.18 to 51.82 ng/ml.
3. There was a significant ($p<0.05$) increase in Lp-PLA2 levels in CAD patients as compared to normal healthy individuals. This change was recorded statistically significant.

They concluded, there is a close relation between Lp-PLA2 and prognosis after CV event. The marker may provide other complementary information about the risk of recurrent stroke and other vascular event.

Our results differs as Rathore et al recruited patients of CAD with stable angina as well as with myocardial infarction. Thus they recorded higher LpPLA2 levels as mentioned previously.

Our study is coherent with results of JUPITER trial sub analysis. LpPLA2 levels correlate with LDL levels and decline with statin treatment. Thus LpPLA2 is not a appropriate marker of CAD

for patients already on statin. Though, it has a role in prognosis of an individual with risk of CAD and its risk factors.

Interest in LpPLA2 has further waned after results of the trials involving inhibition of LpPLA2 with darapladib, namely STABILITY and SOLID TIMI 52 [10] failed to show favorable results. But the jury is still not out on the role of LpPLA2 in determining plaque stability and residual risk. [11]

Limitations

1. Small sample size: Sample size included in this study was only 100 (50 cases and 50 controls). This study shows no trend towards any correlation between LpPLA2 and severity of CAD. However results of this study cannot be extrapolated in general population. Large case control study will be required to confirm our finding.

2. We did not follow the patients or controls. We don't know if raised LpPLA2 levels portend a higher risk of coronary events.

3. Normal levels for LpPLA2 mass levels for Indian population have not been established. This would require studying LpPLA2 levels in healthy population.

Conclusion

- LpPLA2 levels correlate with LDL levels. Levels of LpPLA2 also show reduction after statin treatment along with LDL levels.
- LpPLA2 levels do not correlate with severity of CAD especially in patients on statin treatment.

Recommendation

Based on our study we can recommend that LpPLA2 level may not be measured to assess severity of Coronary artery disease.

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