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# ROLE OF Lp-PLA2 AMONG CORONARY ARTERY DISEASE (CAD) SUBJECTS WITH INFECTIONS

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**ABSTRACT** Coronary Artery Disease (CAD) is defined as a multifactorial disease of coronary blood vessels caused by atherosclerosis, which results in a restriction of blood flow to the heart. Chronic infections have been associated with cardiovascular disease and ischaemic stroke and the association is thought to be the result of chronic low-level inflammation. Emerging risk markers such as Lp-PLA2 are necessary to provide specific value when compared to traditional markers. The association between Lp-PLA2 and infection among CAD patients was not yet studied. Hence, the present study was undertaken to evaluate the role of Lp-PLA2 with history of infections among CAD subjects. Present study consists of 100 individuals suffering with CAD along with a H/o infection as test subjects and 100 age and sex matched healthy subjects as controls. ELISA method was done for estimating Lp-PLA2 concentration. It was observed that, test subjects reported with infections showed an elevated Lp-PLA2 level than the rest. There is an association between infection and Lp-PLA2 level was observed among CAD subjects. This finding suggests that Lp-PLA2 is an efficient prognostic marker for the early prediction of CAD.

**KEYWORDS :** Coronary Artery Disease, Lp-PLA2, infections, Emerging risk makers

## INTRODUCTION

Sanchis-Gomar et al (2016) defined that, "Coronary Artery Disease (CAD) is defined as a multifactorial disease of coronary blood vessels caused by atherosclerosis, which results in a restriction of blood flow to the heart". Fong (2009) reported that, "infectious agents have long been recognized as causes of diseases involving various components of the structure of the heart-- pericardium, muscle, endocardium, valves, autonomic nerves and more recently the vessels of the heart".

Assimes and Roberts (2016) mentioned that, "CAD, with its clinical sequelae of angina, myocardial infarction (MI), heart failure and sudden death, has long been the number 1 cause of death in the developed world". James et al (2018) estimated that, "the global prevalence of CAD was 154 million in 2016, representing 32.7% of the global burden of CV disease and 2.2% of the overall global burden of disease". Esenwa and Elkind (2016) explained that, "chronic infections have been associated with cardiovascular disease and ischaemic stroke and the association is thought to be the result of chronic low-level inflammation". Fong (2009) observed that, "the spectra of microorganisms causing diseases of the heart are very broad and include all classes of microbes". In 2017, Pothineni et al mentioned that, "chronic infections represent one such stimulus that shares the common pathophysiological background of chronic inflammation".

Atik et al (2010) denoted that, "cumulative evidence suggests that Chlamydia pneumoniae also plays an important role in atherosclerosis". In 2014, Morandini et al pointed out that, "Porphyromonas gingivalis (P. gingivalis) is a major contributor to the pathogenesis of periodontitis – an infectious and inflammatory disease that can lead to the destruction of tooth supporting structures, including alveolar bone". Pothineni et al (2017) explained that, "various bacteria and viruses have been shown to have a direct effect on the vascular endothelium as well as an indirect effect by systemic cytokine release, both of which contribute to accelerated atherosclerosis". In 2011, Hayashi et al mentioned that, "chronic periodontitis and P. gingivalis were showed to be associated with lipid metabolic diseases, including atherosclerosis and fatty liver". Pothineni et al (2017) denoted that, "infectious agents that have been linked to atherosclerotic disease include, but not limited to Chlamydia pneumoniae, Porphyromonas gingivalis, Helicobacter pylori, influenza A virus, hepatitis C virus and cytomegalovirus (CMV)".

According to Gazi et al (2011), "regardless of the cause, infection is associated with alterations in lipid and lipoprotein concentrations". Koenig et al (2006) mentioned that, "Lp-PLA2 is a novel marker of inflammation, produced and secreted by monocytes, macrophages, platelets and mast cells, which are all involved in atherogenesis". Atik et al (2010) defined that, "Lp-PLA2 catalyzes the hydrolysis of oxidized LDL, which produces proinflammatory mediators lysophosphatidylcholine (LysoPC) and oxidized fatty acid (oxFA)". Mohler et al (2008) explained that, "lipid metabolism and inflammation have been the major focus of atherosclerosis research for many years, there has been a growing interest in Lp-PLA2 because it is a key enzyme both in lipid metabolism and in stimulating inflammation". Raichlin et al (2008) explained that, "there is a growing body of evidence supporting the major contribution of inflammatory pathways to the etiology of atherosclerosis". Ridker et al (2002) pointed out that, "inflammatory markers improve the prediction of CV risk achieved through the analysis of traditional risk factors alone".

Limited studies reported that, inflammation can be a severe risk factor in CAD patients. No systematic studies were conducted to evaluate the positivity of infectious agents among those with CAD rsik. Emerging risk markers such as Lp-PLA2 are necessary to provide specific value when compared to traditional markers. The association between Lp-PLA2 and infection among CAD patients was not yet studied. Moreover, no study was conducted to rule out the role of infection among subjects with CAD. Hence, the present study was undertaken to evaluate the role of Lp-PLA2 with infections among CAD subjects.

## MATERIALS AND METHODS

One Hundred individuals suffering from CAD and along with a history of infection were selected as test subjects. The samples were referred from Hridayalaya, Institute for Preventive Cardiology, Thiruvanant hapuram to Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, Kerala. One Hundred age and sex matched healthy subjects without any chronic illness was included in control group. Detailed demographic, clinical and lifestyle characteristics were recorded using well-structured proforma. Information about previous infections was also recorded in proforma. In this study, Lp-PLA2 concentrations were quantified in each study subjects. 5ml of blood was collected in plain tube and blood was allowed to cot, serum separated immediately. ELISA method was done for estimating Lp-PLA2 concentration.

## OBSERVATIONS AND RESULTS

The age range of study subjects are from 30 years to 70 years. The

mean age of test and control subjects was 57.14±7.63 and 57.24±8.36 respectively. Test subjects with age ranged from 30 to 50 years showed Lp-PLA2 level of 273ng/mL and for subjects with age ranged from 51 to 70 years showed Lp-PLA2 level of 291ng/mL. Comparatively an increased mean Lp-PLA2 level was observed in test subjects with advanced age range. The observed mean Lp-PLA2 level of test subjects was 276±63.45 and for control subjects it was 113±18.60. A statistically significant difference was observed between the mean Lp-PLA2 level of test and control group with a p value <0.05 (t=24.70).

Distribution of Lp-PLA2 value according to demographic characteristics was given in table 1. In the present study majority of test subjects was male (n=53) and their observed Lp-PLA2 level was higher (286ng/mL) than the female test subjects (266ng/mL). Test subjects who reside in urban area showed an increased Lp-PLA2 level (279ng/mL) than the rest. Out of 100 test subjects, 15 were reported with sedentary type of occupation and their observed Lp-PLA2 concentration was 277ng/mL. Test subjects reported with habit of smoking and alcohol consumption showed an elevated Lp-PLA2 level of 285ng/mL and 297ng/mL. Test subjects reported with obesity showed an increased Lp-PLA2 (312ng/mL) than the non-obese subjects (252ng/mL).

**Table: 1 Distribution of Lp-PLA2 value according to demographic characteristics among test subjects**

| Variables | Category | No. | Lp-PLA2 |
|---|---|---|---|
| Gender | Female | 47 | 226 |
| | Male | 53 | 286 |
| Residence | Urban | 43 | 279 |
| | Rural | 50 | 275 |
| | Coastal | 7 | 274 |
| Type of occupation | Sedentary | 15 | 277 |
| | Non-sedentary | 85 | 272 |
| Smoking | Yes | 23 | 285 |
| | No | 77 | 274 |
| Alcohol consumption | Yes | 26 | 297 |
| | No | 74 | 269 |
| Obesity | Yes | 41 | 312 |
| | No | 59 | 252 |

Distribution of Lp-PLA2 value according to clinical parameters was given in table 2. Test subjects with history of (H/o) Hypertension, H/o Diabetes mellitus, H/o Dyslipidemia showed an increased Lp-PLA2 concentration of 278ng/mL, 292ng/mL and 287ng/mL respectively. Test subjects with H/o Bacterial infection and H/o Dental infection showed an elevated Lp-PLA2 level of 292ng/mL and 279ng/mL respectively.

**Table: 2 Distribution of Lp-PLA2 value according to clinical factors**

| Variables | Category | No. | Lp-PLA2 |
|---|---|---|---|
| H/o Hypertension | Yes | 58 | 278 |
| | No | 42 | 275 |
| H/o DM | Yes | 54 | 292 |
| | No | 46 | 263 |
| H/o Bacterial infection | Yes | 28 | 292 |
| | No | 72 | 270 |
| H/o Dental Infection | Yes | 17 | 279 |
| | No | 84 | 264 |
| H/o Dyslipidemia | Yes | 60 | 287 |
| | No | 40 | 250 |

Distribution of Lp-PLA2 value according to infections was given in table 3. It was observed that, out of 100 test subjects, 26% of test subjects were reported Helicobacter Pyloris positivity, 58% with Helicobacter Pyloris negative and equivocal results were detected in 16% of the test subjects. Helicobacter Pyloris IgG positivity was observed in 32% of test subjects, IgM and AGA positivity was observed in none of the test subjects. Moreover, an elevated Lp-PLA2 level (321ng/mL) was observed among test subjects with Helicobacter Pyloris positivity. Similarly, test subjects reported with Chlamydia Pneumoniae positivity were showed an increased Lp-PLA2 level than the rest. Chlamydia Pneumoniae IgG positivity was reported in 1% test subjects whereas, IgM and IgA were not observed.

Poryphyromonas gingivalis positivity was reported in 6 test subjects and their observed Lp-PLA2 level was 307ng/mL. CMV positivity was observed in 4% of the test subjects with an increased Lp-PLA2 concentration of 287ng/mL then the rest with CMV negative and borderline risk. In test subjects, CMV IgG positivity and equivocal was reported in 3% and 14%, respectively. CMV IgM positivity was observed in 1% of test subjects and IgM equivocal was detected in 8% of the test subjects. It was observed that, test subjects with Hepatitis C virus (HCV) positivity showed an increased Lp-PLA2 level of 277ng/mL and those with HCV negative (showed) lower Lp-PLA3 level of 274ng/mL.

**Table: 3 Distribution of Lp-PLA2 value according to infections**

| Variables | Category | No. | Lp-PLA2 |
|---|---|---|---|
| Helicobacter Pyloris | Reactive | 26 | 321 |
| | Equivocal | 16 | 295 |
| | Non-reactive | 58 | 256 |
| Chlamydia Pneumoniae | Positive | 1 | 319 |
| | Borderline | 2 | 281 |
| | Negative | 97 | 276 |
| Poryphyromonas gingivalis | Positive | 6 | 307 |
| | Negative | 94 | 275 |
| CMV | Positive | 4 | 287 |
| | Borderline | 18 | 277 |
| | Negative | 78 | 271 |
| HCV | Positive | 7 | 277 |
| | Negative | 93 | 274 |

## DISCUSSION

In the current study, test subjects with CAD showed an elevated mean Lp-PLA2 level (276±63.45ng/mL) than the control subjects (113±18.60ng/mL). Buhlin et al (2009) reported that, "elevated concentrations of inflammatory markers of CVD are found in patients with periodontitis". In 2010, Thompson et al mentioned that, "there is a constant relationship between Lp-PLA2 and the risk of coronary heart disease".

Ge et al (2016) reported that, "there is a positive interaction between Lp-PLA2 and classical risk factors in predicting CAD, especially for age. The proportion of CAD attributable to the interaction between Lp-PLA2 and age was as high as 64%". Huang et al (2017) explained that, "the association between Lp-PLA2 and CAD observed in elderly patients". In the present study test subjects with advanced age showed an increased mean Lp-PLA2 level (291ng/mL) than the control group (273ng/mL).

In 2021, Isaac et al reported that, "gender differences in Lp-PLA2 levels were also found; men had significantly higher levels than women (358.018 ± 77.133 vs. 271.8 ± 51.467ng/ml; $p < 0.001$)". Similarly, result was observed in the present study also. Male test subjects showed an elevated Lp-PLA2 level of 286ng/mL than the female subjects (268ng/mL).

Garg et al (2015) estimated that, "the increased Lp-$PLA_2$ activity could lead to greater risk of CAD among subjects with type II diabetes mellitus". In the current study, test subjects reported with H/o DM, H/o Hypertension and H/o Dyslipidemia showed an increased mean Lp-PLA2 concentration than the rest. Nagel et al (2008) observed, "an increased levels of Lp-PLA2 activity in obese adolescents compared with controls and an association between increased Lp-PLA2 mass concentrations and higher body mass index (BMI) percentiles in children". In the present study, it was observed that test subjects reported with obesity showed an elevated Lp-PLA2 level (312ng/mL) than the others without obesity (252ng/mL). In a study done by, Sakka et al (2015) it was explained that, "there is still lack of evidence concerning the role of Lp-PLA2 in childhood obesity and future CVD risk".

According to Liccardo et al (2019), "Gingivitis and its advanced stage, chronic periodontitis, are the most prevalent microbial infections in man". In the current study, Poryphyromonas gingivalis was reported in 6% of the test subjects with an increased Lp-PLA2 concentration of 307ng/mL. Mesa et al (2019) observed, "an association between periodontal diseases and systemic conditions such as coronary heart disease and stroke". Bohnstedt et al (2010) reported that, "different P. gingivalis strains do elicit different levels of IgG, depending on a patient's cardiovascular (CV) and periodontal health". Azarkar et al (2011) reported that, "74.2% of cases in the case group and 45.2% in

the control group were Helicobacter pylori positive for both IgG. 57.5% (42 patient) of those in the case group and 32.1% (25 people) in the control group were IgG positive against H. pylori. The difference was statistically significant (p=0.002) difference was statistically significant (p=0.002)". Kowalski also reported that, "in homogenous group of patients, those with CAD had significantly higher Helicobacter pylori IgG and CagA seroprevalence (69.79% versus 58.20%) as compared to non-CAD controls (40.62% versus 35.89%)". In the current study, test subjects showed 32% Helicobacter pylori IgG positivity.

In the current study 1% of test subjects were reported with Chlamydia Pneumoniae positivity, 2% were reported with borderline risk and remaining 97% with negative report and their observed mean Lp-PLA2 levels was 319ng/mL, 281ng/mL and 276ng/mL. Di Pietro et al (2013) reported that, "intracellular Chlamydophila pneumoniae infection has been shown to induce ROS in macrophages, endothelial and smooth muscle cells, causing oxidative stress". Moreover, Sessa et al (2014) explained that, "oxidative stress can lead to endothelial dysfunction, foam cell formation, SMC proliferation, platelet aggregation as well as cytokine, growth factor, and cell adhesion molecule production".

In the present study, 7% of test subjects were reported with HCV positivity. El Sagheer et al (2018) suggested that, "HCV infection provokes fatty liver infiltration, insulin resistance (IR), type 2 diabetes mellitus (DM) and atherosclerosis, which are known complications of the metabolic syndrome, despite a paradoxically "protective" serum lipid profile characterized by optimal or low low-density lipoprotein (LDL) and total cholesterol levels". Babiker et al (2017) reported that, "HCV infection increases CVD risk through several mechanisms, including insulin resistance, hepatic steatosis and increased chronic inflammation and immune activation". According to Caini et al (2007), "HCV infection could influence Lp-PLA2 plasma activity". Guerra et al (2007) mentioned that, "HCV-infected patients showed a significant decrease of this enzyme activity that was only recovered by viral clearance after antiviral treatment". In the current study, test subjects reported with HCV positivity showed a mean Lp-PLA2 level (277ng/mL) higher than the rest.

In a previous study done by, Qiao et al (2000) reported that, "cigarette smoking is an independent risk factor for atherosclerosis and coronary heart disease". Manafa et al (2019) revealed that, "cigarette smoking influenced plasma Lp-PLA2 in peripheral blood mononuclear cells (PBMC), through the induction of oxidative stress". According to Fratta Pasini et al (2013), "a positive correlation between Lp-PLA2 activity and circulating oxidized low-density lipoprotein (oxLDL) has been demonstrated in a hypercholesterolemic swine model of atherosclerosis". Athyros et al in (2013) reported that, "oxLDL can up-regulate the expression of Lp-PLA2 in human monocyte-derived macrophages". In the current study test subject with habit of smoking and alcohol consumption showed an elevated Lp-PLA2 concentration of 285ng/mL and 297ng/mL respectively. Manafa et al (2019) explained that, "a positive correlation existed between the serum levels of Lp-PLA2 and duration of smoking (years). Same pattern was also observed between the serum levels of Lp-PLA2 and age in adult male cigarette smokers".

## CONCLUSION

In conclusion, results from the current study showed that, patients with CAD showed an increased concentration of Lp-PLA2 than the control subjects. Moreover, test subjects reported with infections also showed an elevated Lp-PLA2 level than the others without infection. In short, there was a strong association between seropositivity and Lp-PLA2 level was observed among the test subjects. There is an association between infection and Lp-PLA2 level was observed among CAD subjects. The present study indicates that, Lp-PLA2 plays an important role in the occurrence and development of CAD. Dynamic evaluation of Lp-PLA2 level provides prognostic value on CAD risk assessment along with infections. Increased CVD risk during infection is a growing concern and measures to minimize this risk are urgently needed. This finding suggests that Lp-PLA2 is an efficient prognostic marker for the early prediction of CAD.

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