DOI: 10.7860/JCDR/2022/55726.16681

Original Article

Biochemistry Section

Role of Lipoprotein Associated Phospholipase A2 in Diagnosis of Coronary Artery Disease

V VEENA[1], M GANESH[2], SANTHI SILAMBANAN[3]

ABSTRACT

Introduction: Cardiovascular Diseases (CVD) are a major cause of significant morbidity and mortality in industrialised countries, of which Coronary Artery Disease (CAD) is the most common. The diagnostic workup of CAD has improved over the years starting from conventional investigations like Electrocardiography (ECG) to invasive procedures like coronary angiogram. Moving forward, numerous novel inflammatory biomarkers are coming up to diagnose CAD.

Aim: To assess the role of Lipoprotein associated Phospholipase A2 (LpPLA2) as an independent predictor of CAD.

Materials and Methods: This case-control study was conducted in the Inpatient Department of Cardiology at Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India, from September 2014 to November 2014. Participants without significant blockage in the coronary arteries and without detectable atheroma served as controls and those with detectable atheroma and significant blockage in coronary arteries served as cases. Peripheral blood samples of 80 male patients aged over 40 years undergoing Coronary Angiography were processed for LpPLA2 levels. Mean and Standard deviation was calculated for the parameters included in the study. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 15.0.

Results: Mean age of the participants in the control group was 51.75±8.74 years and that of the case group was 59.15±11.31 years. The mean LpPLA2 level in the cases was found to be higher than that in the controls and the difference was statistically significant (p-value <0.05). No correlation was noted between the age and Body Mass Index (BMI) of both the groups with their respective LpPLA2 levels.

Conclusion: The current study showed that LpPLA2 can be used as a potential independent predictor of CAD, thus minimising the usage of invasive investigations and favouring the psychosocial and economic welfare of the patients.

Keywords: Age, Biomarkers, Body mass index, Cardiovascular diseases, Inflammation

INTRODUCTION

Cardiovascular Diseases (CVD) rank first among the causes of significant morbidity and mortality in industrialised countries, of which Coronary Artery Disease (CAD) is the most common [1]. Coronary artery disease presents with a characteristic set of symptoms such as chest pain or discomfort which starts in the centre or left side of the chest, radiating to the shoulders and sometimes to the upper limbs, dyspnoea, nausea, giddiness etc. Sometimes, this pain mimics indigestion or heartburn and goes unnoticed. In a smaller fraction of people, it is asymptomatic and is called a silent CAD [2]. The diagnostic workup of CAD includes a complete and extensive elicitation of history to exclude the anticipated risk factors, a thorough clinical examination, risk scoring systems, blood investigations such as lipid profile and certain biomarkers, chest X-ray, electrocardiogram, echocardiogram, ultrasound imaging of coronary vasculature, coronary angiogram and nuclear imaging [3].

Traditional risk factors for CVD include dyslipidemia, diabetes mellitus, hypertension, smoking, alcoholism, obesity, sedentary lifestyle and unhealthy dietary habits [4]. In addition, psychosocial stress also plays a major role in the causation of the disease [5]. A parental family history of death due to CAD is associated with a higher risk in both men and women [6]. All these risk factors have an independent tendency to predispose to the pathogenesis of CAD by promoting inflammatory processes in the coronary vasculature. A number of risk scoring systems such as Framingham risk score, Prospective Cardiovascular Munster (PROCAM) scores and Systematic Coronary Risk Evaluation (SCORE) scores are being followed to stratify the future risk of coronary events [7]. Since inflammation and atherosclerosis play a central role in causation of CAD, many inflammatory markers such as C-Reactive Protein (CRP), Interleukin-1(IL-1), fibrinogen, homocysteine etc have come up which are being routinely used for Cardiovascular (CV) risk stratification [8]. There are a few novel biomarkers like Lipoprotein-associated Phospholipase A2 (LpPLA2), Placental growth factor etc which are under the process of research for screening and diagnosis of CAD [4,9].

The LpPLA2, also known as Platelet Activating Factor Acetyl Hydrolase (PAF-AH) is a recently discovered, potentially useful biomarker for CVD. LpPLA2 has an active site made up of Serine, Histidine and Aspartic acid triad [10], unlike the other phospholipases which have dyads. The C-terminal of this enzyme is found to be required for its binding to High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL). LpPLA2 circulates in the blood mainly in association with LDL, HDL and also with Lipoprotein-a (Lp-a). Majority of the LDL associated LpPLA2 is bound to the atherogenic small dense LDL. It has two prominent biological activities viz., it inactivates the potent proinflammatory mediator, Platelet Activating Factor (PAF) and it hydrolyses the oxidatively modified polyunsaturated fatty acids, to produce Lysophosphatidyl choline (LysoPC) and oxidised Non Esterified Fatty Acids (ox NEFA) [10]. The LysoPC upregulates certain proinflammatory cytokines, adhesion molecules and Monocyte Chemoattractant Protein-1 (MCP-1) and ox NEFA has potent monocyte chemoattractant property, thus, promoting inflammation.

It has been proved that the factor which determines the role of LpPLA2 in atherosclerosis, proatherogenic or antiatherogenic, is the type of lipoprotein with which it is associated. While it is found that LDL-associated- LpPLA2 has a positive relationship with the risk of future cardiac events, HDL associated LpPLA2 and Lp-a associated LpPLA2 are found to be antiatherogenic [11]. However, there is no adequate literature that established a relation between LpPLA2

and subclinical atherosclerosis [12]. Thus, the inclusion of patients with normal coronary arteries on angiography had an advantage over population-based controls, as it ruled out the presence of subclinical coronary disease. The aim of this study is to assess the role of LpPLA2 as an independent predictor of CAD.

Objectives:

- To estimate the serum level of LpPLA2 in the controls as well as cases of CAD who had undergone coronary angiography.
- To find whether there is any statistically significant difference in LpPLA2 levels between the controls and cases and to assess the correlation between the age and BMI of both the groups with their respective LpPLA2 levels.

MATERIALS AND METHODS

This case-control study was conducted in the Inpatient Department of Cardiology at Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India, from September 2014 to November 2014. The study was performed in agreement with specifications as recommended by the Institutional Ethics Committee, Sri Ramachandra Medical College and Research Institute (Ref: CSP-MED/14/SEP/18/165). A written informed consent was obtained from each participant before commencement of the study. The study included 80 males undergoing coronary angiography. Subjects were chosen based on convenient sampling. Out of 110 selected study participants (after including 40 as cases and 40 as controls), 20 cases and 10 controls were excluded.

- **Control group** (n=40): All participants without significant blockage in the coronary arteries and without detectable atheroma.
- **Cases group** (n=40): All participants with detectable atheroma and significant blockage in coronary arteries.

Inclusion criteria: Male patients, aged >40 years having hypertension and hyperlipidaemia. The reason for choosing male patients was the higher levels of LpPLA2 (more than 200 ng/mL) and thus a greater correlation found in males compared to females in the previous studies [4]. Inadequate number of female patients admitted for coronary angiogram during that particular period was another reason.

Exclusion criteria: Female patients and patients with diabetes mellitus, renal disease, chronic inflammation or infection, previous history of coronary artery intervention, malignancy or thyroid disorders were excluded from the study.

Procedure

The patient data was collected through case reports. All patients were interviewed for a full medical history including age (years), family history of diabetes, hypertension and dyslipidemia. A thorough elicitation of clinical history was done which revealed history of symptoms like profuse sweating, left sided chest pain, vague chest discomfort, left shoulder pain, back pain, and palpitations. The general physical examination included measurement of height, weight and vital signs including pulse rate and blood pressure. BMI was calculated using the formula:

$$\text{BMI} = \text{Weight in (kilograms)} / \text{Height in (metres}^2\text{)}$$

The controls and cases were divided into two groups based on BMI (BMI <25 kg/m^2 and BMI >25 kg/m^2).

Peripheral venous blood samples of about 3 mL were collected under strict aseptic conditions, from all the 80 participants. The samples were collected in yellow topped serum separator tubes and incubated for 30 minutes for clot formation at 28° to 30°C and centrifuged at 3500 rpm for 5 minutes. Serum samples of 0.5 to 1 mL were taken in eppendorfs, labeled appropriately and stored at -20°C. Human serum LpPLA2 was measured using R&D systems Human PLA2G7/PAF-AH/Lp-PLA2 Quantikine Enzyme-Linked Immunosorbent Assay (ELISA) Kit, catalogue number DPLG70 following the kit instructions. This assay employs the quantitative sandwich enzyme immunoassay technique.

STATISTICAL ANALYSIS

Mean and standard deviation was calculated for the parameters included in the study. Independent student unpaired t-test was performed to determine whether there is a statistically significant difference between parameters among the two groups. Pearson's correlation coefficient was used to assess the relationship between the variables and to assess the strength and direction of association between two variables. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago. IL, USA).

RESULTS

The clinical and demographic characteristics of both cases and controls were tabulated in [Table/Fig-1]. Mean age of the participants in the control group was 51.75±8.74 years and that of the case group was 59.15±11.31 years. The distribution of the study participants based on their presenting symptoms is shown in [Table/Fig-2]. Majority (42.5%) of controls were in the age group of 40-50 years and 40% of cases were in the age group 61-70 years. Mean height of cases and controls were 162.28±7.96 cm and 158±7.67 cm (p-value=0.86) and mean weight were 74.72±13.53 kg and 64.63±9.95 kg (p-value=0.003). About 47.5% of controls had a BMI <25 kg/m^2 and 92.5% of cases had a BMI >25 kg/m^2 [Table/Fig-3]. The mean age as well as BMI of

Parameter	Cases (Mean±SD)	Controls (Mean±SD)	p-value (Unpaired student's t-test)
Age (years)	59.15±11.31	51.75±8.74	0.002
BMI (kg/m^2)	28.23±3.88	26±4.4	0.02
Pulse rate (/min)	82.1±5.85	76.2±5.98	0.0001
Blood pressure			
Systolic blood pressure (mmHg)	142.4±9.27	128.2±5.16	0.0001
Diastolic blood pressure (mmHg)	90.3±6.26	84.05±5.80	0.0001
LpPLA2 (ng/mL)	252.13±94.61	114.34±76.47	<0.05
Family history n (%)			
Diabetes mellitus	25 (62.5%)	13 (32.5%)	-
Hypertension	24 (60%)	10 (25%)	-
Dyslipidemia	26 (65%)	14 (35%)	-

[Table/Fig-1]: Demographic and clinical characteristics of cases and controls. p-value <0.05 was considered as statistically significant

Variables	Cases n (%)	Controls n (%)
Sweating	9 (22.5)	5 (12.5)
Left sided chest pain	21 (52.5)	2 (5)
Chest discomfort	1 (2.5)	22 (55)
Left shoulder pain	2 (5)	-
Back pain	3 (7.5)	9 (22.5)
Palpitations	4 (10)	2 (5)

[Table/Fig-2]: Distribution based on presenting symptoms in cases and controls.

Variables	Controls (n, %)	Cases (n, %)
BMI (kg/m^2)		
<25	19 (47.5)	3 (7.5)
>25	21 (52.5)	37 (92.5)
Age (years)		
40-50	17 (42.5%)	11 (27.5%)
51-60	16 (40%)	8 (20%)
61-70	6 (15%)	16 (40%)
>70	1 (2.5%)	5 (12.5%)

[Table/Fig-3]: Distribution of age and Body Mass Index (BMI) among controls and cases.

cases was found to be higher when compared to those of controls. The mean LpPLA2 level in the cases was found to be higher than that in the controls and the difference was statistically significant (p-value <0.05) [Table/Fig-1].

Correlation between LpPLA2 levels with age and BMI in both the groups as well as in the overall subjects were assessed and was not found to be statistically correlated [Table/Fig-4-6].

Group	Age (years)	LpPLA2 (ng/mL)	Pearson's correlation coefficient	p-value
Controls	51.75±8.74	114.34±76.47	-0.035	0.830
Cases	59.15±11.31	252.13±94.61	-0.089	0.584

[Table/Fig-4]: Correlation between age and LpPLA2 between the groups.
p-value <0.05 was considered as statistically significant

Group	BMI (kg/m^2)	LpPLA2 (ng/mL)	Pearson's correlation coefficient	p-value
Controls	26±4.4	114.34±76.47	0.135	0.406
Cases	28.23±3.88	252.13±94.61	-0.191	0.237

[Table/Fig-5]: Correlation between BMI and LpPLA2 between groups.
p-value <0.05 was considered as statistically significant

Parameters	LpPLA2 (ng/mL)		Pearson's correlation coefficient	p-value
	Control (Mean±SD)	Cases (Mean±SD)		
Age (years)	55.45±10.71837	190.92±133.39	0.175	0.278
BMI (kg/m^2)	27.12125±4.305125	190.92±133.39	0.122	0.452

[Table/Fig-6]: Correlation of age and BMI with LpPLA2 levels in overall subjects.
p-value <0.05 was considered as statistically significant

DISCUSSION

Coronary artery disease has been recognised as the most common of the cardiovascular diseases, which account for majority of the morbidity and mortality in developed as well as developing countries. There is extensive evidence available linking the aetiopathogenesis of CAD to inflammation and atherosclerosis [13]. The initial trigger for inflammation and thus atherosclerosis is vascular endothelial injury. This leads to an imbalance between vasodilator and vasoconstrictor substances and endothelial cell activation, thus promoting atherosclerosis [14]. CAD presents with a typical set of symptoms such as pain in left side or centre of the chest, radiating to left shoulder and back, dyspnoea etc. At times, these symptoms are subclinical, mimicking heartburn or indigestion, leading to a missed diagnosis [15].

As stated earlier, inflammation and atherosclerosis are the key factors in the causation of CAD and many inflammatory markers like hs-CRP, homocysteine, Interlukin-1, are being used as markers for cardiovascular risk stratification [8]. However, all these conventional markers used are not specific for cardiac disease and have their own limitations. Hence, they cannot be adopted for routine clinical use. Thus, there is a need for a cardiac specific marker which can aid in the early diagnosis and risk stratification of CAD. Lipoprotein associated Phospholipase A2 (LpPLA2) is one such novel biomarker of CAD.

LpPLA2, also known as PAF-AH is a phospholipase enzyme, which, in humans is encoded by PLA2 G7 gene. Its synthesis is regulated by various inflammatory cytokines such as Interferon-γ and lipopolysaccharides at the transcriptional level [16]. The LpPLA2 has limited expression in leukocytes and unstimulated monocytes, whereas, it is induced during differentiation to macrophages and in foam cells [17]. It has two prominent biological activities like, inactivation of the potent proinflammatory mediator PAF (antiatherogenic), and hydrolysis of the oxdatively modified polyunsaturated fatty acids, to produce proinflammatory mediators such as LysoPC and ox NEFA (proatherogenic). However, a large body of evidence favours the proatherogenic property of LpPLA2 [18,19].

The present study was primarily aimed at determining the ability of LpPLA2 to detect the presence of CAD, thus negating the need for invasive diagnostic procedures like Coronary Angiogram. Sabatine MS et al., in his study have found LpPLA2 as a superior marker of CAD, when compared to other traditional markers such as high sensitivity C-Reactive Protein (hsCRP) and Homocysteine (HCY) [20]. Packard CJ et al., in their study has found LpPLA2 associated with the risk of CAD and not being confounded by factors like age, systolic blood pressure [18]. Bhatti S et al., have found that the latest evidence are in favour of LpPLA2 in determination of cardiovascular risk over the conventional risk factors and biomarkers [19]. Thus, several previous studies have established the potential of LpPLA2 as a marker of CAD, which kindled the interest and curiosity to assess its levels in the CAD patients admitted in our hospital [18,19,20].

Brilakis ES et al., has shown an association between LpPLA2 levels and severe angiographic CAD along with many other authors [4,21]. Moreover, Rotterdam study, which was done in an attempt to assess the relationship of LpPLA2 with subclinical atherosclerosis, had failed to establish the same [12]. Thus, the inclusion of patients with normal coronary arteries on angiography had an advantage over population-based controls, as it ruled out the presence of subclinical coronary disease.

The present study population included 80 participants (male), of which 40 were controls and 40 were cases. The reason for choosing male, is the higher levels of LpPLA2 and thus a greater correlation were found in men compared to women in the previous studies [4,22]. Brilakis ES et al., showed a significant difference between males and females in his studies (p-value <0.003 and p-value <0.001, respectively) [4,22]. The reason for the lower levels in women is believed to be due to the negative regulatory effect of their high oestrogen levels on LpPLA2 mass and activity [23]. West of Scotland Coronary Prevention Study (WOSCOPS) which was similarly done exclusively in males, had found LpPLA2 as an independent predictor of cardiovascular risk, which was not associated with other traditional risk factors like CRP, fibrinogen, white blood cell count, age, triglycerides, LDL, HDL and hypertension [18].

Several lines of evidence showing elevated LpPLA2 levels due to the presence of Rheumatoid Arthritis (RA) [24] and Non Alcoholic Fatty Liver Disease (NAFLD) are available [25]. Though the present study population did not include patients with such conditions, there is always a possibility for the presence of subclinical manifestations of these disorders.

The mean and standard deviation of LpPLA2 level in the controls group was 114.34±76.47 ng/mL and in cases was 252.13±94.61 ng/mL [Table/Fig-1]. A statistically significant difference was observed in the LpPLA2 levels of controls and cases groups (p-value <0.05). This is in agreement with the results of several other previous studies done with the aim of determining the potential of LpPLA2 to be a biomarker of CAD [Table/Fig-7].

Author of study	Study design	Place and year of publication	LpPLA2 level (cases/controls)
Oei HS et al., [12]	Case cohort study	Rotterdam, Netherlands, 2005	49±11/44±12*
Packard CJ et al., [18]	Case-control study	Scotland, 2000	2.37±0.52/2.27±0.57 (mg/L)
Sabatine MS et al., [20]	Case cohort study	Massachusetts, United States of America, 2007	222.4 ng/mL
Daniels LB et al., [26]	Case-control study	California, United States of America, 2008	538±180/494±167°
Nambi V and Ballantyne CM [27]	Case cohort study	Texas, United States of America, 2006	404/373 µg/L^
Jenny NS et al., [28]	Case cohort study	Vermont, United States of America, 2010	340/360°

Mourouzis K et al., [29]	Cross-sectional study	Athens, Greece, 2021	99/154 µg/L
Kumar D et al., [30]	Case-control study	Uttar Pradesh, India, 2017	737±224/556±29
Present study	Case-control study	Tamil Nadu, India 2022	252.13±94.61/ 114.34±76.47°

[Table/Fig-7]: Previous studies on LpPLA2 and their results.
*LpPLA2 activity nmol/min/ml, °LpPLA2 mass ng/mL
^Age, sex and race adjusted mean/proportion

In the current study, a statistically significant difference was noted between the age and BMI of controls and cases (p-value=0.002 and p-value=0.02 respectively). However, the correlation between age as well as BMI with LpPLA2 levels in both the controls group (p-value=0.830, p-value=0.406) and the cases group (p-value=0.584, p-value=0.237) was not statistically significant. Similar results were obtained by other authors in their study (p-value was 0.92 and 0.91 for the correlation between age and BMI with LpPLA2 levels respectively) [4]. Thus, age and BMI are not associated with LpPLA2 levels in controls as well as cases.

The advantage of LpPLA2 over other inflammatory markers such as CRP, fibrinogen is that it is not influenced by factors like chronic inflammation, obesity and insulin resistance and can be used as a potentially independent marker which is directly involved in atherogenesis [18]. Elevated LpPLA2 levels are also found to independently predict adverse cardiovascular outcomes [20].

Thus, the advent of such a novel, independent, less biovariable, cardiac specific marker can be effectively used in early detection and risk stratification of CAD, thus leading to a significant reduction in the associated morbidity and mortality rates.

Limitation(s)

Female study participants were not included and the correlation of parameters like diabetes, hypertension and dyslipidemia with LpPLA2 levels were not studied.

CONCLUSION(S)

In view of the statistically significant difference between the LpPLA2 levels in the controls and cases groups and due to the lack of association of LpPLA2 levels with age and BMI, LpPLA2 may be useful as a potential independent predictor of CAD and thus, reduced usage of invasive procedures like coronary angiogram might eventually have a positive effect on the psychosocial and economic welfare of the patients. This study may be done with a larger sample size and correlation with severity of CAD may be studied in future studies.

Acknowledgement

Authors are thankful to all the staff of the tertiary care hospital, all the patients who participated in the study, R&D Diagnostics and last but not the least, the Almighty God.

REFERENCES

[1] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 study. Journal of the American College of Cardiology. 2020;76(25):2982-3021.
[2] Cohn PF, Fox KM, Daly C. Silent myocardial ischemia. Circulation. 2003;108(10):1263-77.
[3] Cassar A, Holmes Jr DR, Rihal CS, Gersh BJ. Chronic coronary artery disease: Diagnosis and management. In Mayo Clinic Proceedings. Elsevier. 2009;84(12):1130-46.
[4] Brilakis ES, McConnell JP, Lennon RJ, Elesber AA, Meyer JG, Berger PB, et al. Association of lipoprotein - associated phospholipase A2 levels with coronary artery disease risk factors, angiographic coronary artery disease, and major adverse events at follow-up. Eur Heart J. 2005;26(2):137-44. Available from http://www.ncbi.nlm.nih.gov/pubmed/15618069.
[5] Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk facto rs in cardiac practice: The emerging field of behavioural cardiology. J Am Coll Cardiol. 2005;45(5):637-51.
[6] Schildkraut JM, Myers RH, Cupples LA, Kiely DK, Kannel WB. Coronary risk associated with age and sex of parental heart disease in the Framingham Study. Am J Cardiol. 1989;64(10):555-59. Available from: http://linkinghub.elsevier.com/retrieve/ pii/0002914989904773.
[7] Tolunay H, Kurmus O. Comparison of coronary risk scoring systems to predict the severity of coronary artery disease using the SYNTAX score. Cardiol J. 2016;23(1):51-56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26503075.
[8] Madjid M, Willerson JT. Inflammatory markers in coronary artery disease. British Medical Bulletin. 2011;100(1):23-28.
[9] Marković M, Ignjatović S, Majkić-Singh N, Dajak M. Placental growth factor in acute coronary syndrome patients with non ST-elevation. Laboratory Medicine. 2009;40(11):675-78.
[10] Kyoung-Rok Do, Kim AC, Chang AB, Seong SA, Shin JM, Sang-Jun Yea, et al. Darapladib binds to lipoprotein-associated phospholipase A2 with meaningful interactions. Bulletin of the Korean Chemical Society. 2014;35(1):250-52.
[11] Tellis CC, Tselepis AD. The role of lipoprotein - associated phospholipase A2 in atherosclerosis may depend on its lipoprotein carrier in plasma. Biochem Biophys Acta. 2009;1791(5):327-38. Available from: http:// www.ncbi.nlm. nih.gov/ pubmed/ 19272461.
[12] Oei HS, van der Meer IM, Hofman A, Koudstaal PJ, Stijnen T, Breteler MMB, et al. Lipoprotein-associated phospholipase A2 activity is associated with risk of coronary heart disease and ischemic stroke: The Rotterdam Study. Circulation. 2005;111(5):570-75. Available from: http://www.ncbi.nlm. nih.gov/pubmed/15699277.
[13] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352(16):1685-95.
[14] Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation. 2004;109(23 Suppl 1):III27-32.
[15] Kuller LH, Shemanski L, Psaty BM, Borhani NO, Gardin J, Haan MN, et al. Subclinical disease as an independent risk factor for cardiovascular disease. Circulation. 1995;92:720-26.
[16] Cao Y, Stafforini DM, Zimmerman GA, McIntyre TM, Prescott SM. Expression of plasma platelet-activating factor acetyl hydrolase is transcriptionally regulated by mediators of inflammation. J Biol Chem. 1998;273(7):4012-20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9461591.
[17] Ferguson JF, Hinkle CC, Mehta NN, Bagheri R, Der Ohannessian SL, Shah R, et al. Translational studies of lipoprotein- Associated phospholipase A2 in inflammation and atherosclerosis. J Am Coll Cardiol. 2012;59(8):764-72.
[18] Packard CJ, O'Reilly DS, Caslake MJ, McMahon AD, Ford I, Cooney J, et al. Lipoprotein- associated phospholipase A2 as an independent predictor of coronary heart disease. N Engl J Medicine. 2000;343(16):1148-55.
[19] Bhatti S, Hakeem A, Cilingiroglu M. Lp-PLA2 as a marker of cardiovascular diseases. Curr Atheroscler Rep. 2010;12(2):140-44. Available from: http://link.springer.com/10.1007/s11883-010-0095-6.
[20] Sabatine MS, Morrow DA, O'Donoghue M, Jablonksi KA, Rice MM, Solomon S, et al. Prognostic utility of lipoprotein- associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. Arteriosclerotic hromb Vasc Biol. 2007;27(11):2463-69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17766330.
[21] Caslake MJ, Packard CJ, Suckling KE, Holmes SD, Chamberlain P, Macphee CH, et al. Lipoprotein-associated phospholipase A(2), platelet- activating factor acetyl hydrolase: A potential new risk factor for coronary artery disease. Atherosclerosis. 2000;150(2):413-19. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10856534.
[22] Brilakis ES, Khera A, McGuire DK, See R, Banerjee S, Murphy SA, et al. Influence of race and sex on lipoprotein- associated phospholipase A2 levels: Observations from the Dallas Heart Study. Atherosclerosis. 2008;199(1):110-15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18061193.
[23] Miyaura S, Maki N, Byrd W, Johnston JM. The hormonal regulation of platelet-activating factor acetyl hydrolase activity in plasma. Lipids. 1991;26(12):1015-20.
[24] Södergren A, Karp K, Bengtsson C, Möller B, Dahlqvistand SR, Jonsson SW. Is lipoprotein-associated phospholipase A2 a Link between inflammation and subclinical atherosclerosis in rheumatoid arthritis? Bio Med Research International. 2015. Article ID 673018. http://dx.doi.org/10.1155/2015/673018.
[25] Colak Y, Senates E, Ozturk O, Doganay HL, Coskunpinar E, Oltulu YM, et al. Association of serum lipoprotein- associated phospholipase A2 level with non-alcoholic fatty liver disease. Metab Syndr Relat Disord. 2012;10(2):103-09. Doi: 10.1089/met.2011.0111. Epub 2011.
[26] Daniels LB, Laughlin GA, Sarno MJ, Bettencourt R, Wolfert RL, Barrett-Connor E, et al. Lipoprotein- associated phospholipase A2 is an independent predictor of incident coronary heart disease in an apparently healthy older population: The Rancho Bernardo Study. J Am Coll Cardiol. 2008;51(9):913-19. Available from: http:// www. ncbi. nlm.nih. gov/pubmed/18308160.
[27] Nambi V, Ballantyne CM. Lipoprotein- associated phospholipase A2: Pathogenic mechanisms and clinical utility for predicting cardiovascular events. Curr Atheroscler Rep. 2006;8(5):374-81. Available from: http://link.springer. com/10.1007/s11883-006-0034-8.
[28] Jenny NS, Solomon C, Cushman M, Tracy RP, Nelson JJ, Psaty BM, et al. Lipoprotein- associated phospholipase A2 (Lp-PLA_2) and risk of cardiovascular disease in older adults: Results from the Cardiovascular Health Study. Atherosclerosis. 2010;209(2):528-32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19804.

[29] Mourouzis K, Siasos G, Oikonomou E, Zaromitidou M, Tsigkou V, Antonopoulos A. Lipoprotein associated Phospholipase A2 levels, endothelial dysfunction and arterial stiffness in patients with stable coronary artery disease. Lipids Health Dis. 2021;20:12.

[30] Kumar D, Mishra AK, Siddiqui MS, Qureshi A. Study of lipoprotein-associated phospholipase A2 and carotid intima media thickness as markers of increase cardiovascular risk. International Journal of Contemporary Medical Research. 2017;4 (5):1083-85.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Biochemistry, Saveetha Medical College, Thandalam, Kanchipuram, Tamil Nadu, India.
2. Head, Department of Biochemistry, Sri Ramachandra Medical College, Chennai, Tamil Nadu, India.
3. Professor, Department of Biochemistry, Sri Ramachandra Medical College, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. V Veena,
Assistant Professor, Department of Biochemistry, Saveetha Medical College,
Thandalam, Kanchipuram, Tamil Nadu, India.
E-mail: drveenanobel@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 05, 2022
- Manual Googling: May 07, 2022
- iThenticate Software: May 17, 2022 (9%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 23, 2022**
Date of Peer Review: **Mar 10, 2022**
Date of Acceptance: **May 09, 2022**
Date of Publishing: **Aug 01, 2022**