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Role of Lp-PLA2 and hsCRP in the Early Prediction of Coronary Artery Disease (CAD)

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Abstract

CAD is a multifactorial disease caused by the interaction among the variables, incorporating non-modifiable and modifiable risk factors, which brings people at a higher risk of CAD. The global prevalence of CAD was 154 million in 2016. There are several conventional markers which were used for the early prediction of CAD. Even though emerging risk markers are necessary to provide specific value when compared to traditional markers. hsCRP and Lp-PLA2 is implicated in several atherosclerosis phases. However, there is no systematic studies were conducted to evaluate the role of hsCRP and Lp-PLA2 in CAD. Hence the current study was undertaken to analysis the role of Lp-PLA2 and hsCRP in the early prediction of CAD. The present study consists of 150 test subjects with CAD and 100 healthy age and sex matched individuals as control. It was concluded that, a higher Lp-PLA2 and hsCRP level were associated with a higher incidence of major adverse events of CAD risk factors

Keywords: Coronary Artery Disease, Lp-PLA2, hsCRP

Introduction

According to Centers for Disease control and prevention (CDC) (2021), "coronary artery disease (CAD) occurs by plaque formation in the wall of the arteries (called coronary arteries) which carries blood to the heart". Garko (2013) suggested that, "CAD is a multifactorial disease caused by the interaction among the variables, incorporating non-modifiable and modifiable risk factors, which brings people at a higher risk of CAD". 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". Aggarwal et al (2016) reported that, "ethnic wise south Asians especially Indians are more vulnerable to have CAD in young age group with a prevalence of 5% to 10%".

Ridker et al (2009) explained that, "biomarker predicts Cardiovascular (CV) events in healthy people as well as in those with atherosclerotic disease". According to Bhagwat et al (2015), "earlier the diagnosis of CAD depends on conventional risk factors. Conventional risk factors like smoking, hypertension, diabetes are reported to 50% of prevalence and severity of the disease". Acevedo et al (2015) suggested that, "High sensitivity C-reactive

protein (hsCRP) is a good predictor of metabolic syndromes and is strongly associated with abdominal obesity". In 2015, Kamath et al pointed out that, "some studies have evaluated the association of hsCRP and risk factors for CVD and diabetes mellitus". Krishnamoorthy et al (2021) suggested that, "serum levels of hsCRP may serve as a predictor of long-term stroke recurrence risk in symptomatic intracranial atherosclerotic disease". Ali and Madjid (2009) explained that, "Lipoprotein-associated phospholipase A_2 (Lp-PLA2) is a novel inflammatory marker that has been the recent focus of multiple epidemiologic studies". Mannheim et al (2008) mentioned that, "Lp-PLA2, an enzyme expressed by inflammatory cells in atherosclerotic plaques, is carried in the circulation bound predominantly to LDL". Madjid et al (2010), "a growing body of evidence suggests that Lp-PLA_2 is a CV risk marker independent of traditional risk factors".

In 2011, Colley et al mentioned that, "Lp-PLA2 is implicated in several atherosclerosis phases and can be a good biomarker for estimating clinical CAD outcomes". Krishnamoorthy et al (2021) suggested that, "elevation of hs-CRP and Lp-PLA2 correlated with the severity of stenosis in symptomatic intracranial atherosclerotic disease". No systematic studies were conducted to evaluate the role of hsCRP and Lp-PLA2 in CAD patients. Hence the current study was undertaken to analysis the role of Lp-PLA2 and hsCRP in the early prediction of CAD.

Materials And Methods

Hundred fifty test subjects suffering with CAD were selected for this study. The samples were referred from Hridayalaya, Institute for Preventive Cardiology, Thiruvananthapuram 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. In this study, hsCRP and 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. Lipid profile was estimated using semi-automated clinical chemistry analyzer. Turbidometric Method was to quantify the hsCRP level and ELISA method was done for estimating Lp-PLA2.

Observations And Results

The age range of study subjects was from 30 years to 70 years. The mean age of test and control subjects was 57.26±8.27 and 57.19±8.02 respectively. No statistical significant difference was observed between the mean age of test and control subjects. Test group consist of 53% (n=79) of male subjects and 47% (n=71) of female subjects. Test subjects showed a mean hsCRP concentration of 3.09±0.99 and for control subjects it was 1.75±0.84. A statistically significant difference was observed between the mean hsCRP level among study subjects ($t=11.043$; $p<0.05$). The observed mean Lp-PLA2 level of test and control subjects was 280±63.52 and 159±26.06 respectively. Moreover, a statistically significant difference of Lp-PLA2 level was observed between the test and control subjects with a p value <0.05 ($t=18.10$). An elevated concentration of hsCRP and Lp-PLA2 was observed among the test subjects when compared to the control. Thus hsCRP and Lp-PLA2 has strong positive association with CAD.

Distribution of hsCRP and Lp-PLA2 value according to demographic characteristics was given in the below table 1. Among 150 test subjects, 120 subjects within the age range of 51-70 years showed an increased mean hsCRP and Lp-PLA2 level of 3.10mg/L and 281ng/mL respectively. The mean hs CRP and Lp-PLA2 concentration was comparatively higher in male subjects when compare to the female subjects. Test subjects who reside in coastal area showed decreased hsCRP and Lp-PLA2 concentration compared to the others who residing in urban and rural areas. Test subjects with sedentary type of occupation showed a mean hsCRP value of 3.42 mg/L and Lp-PLA2 value of 280ng/mL. Those who reported with sedentary type of occupation showed an increased mean hsCRP and Lp-PLA2 concentration when to the rest.

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Table: 1 Distribution of hsCRP and Lp-PLA2 value according to demographic characteristics among study subjects

Variables	Category	No.	hsCRP	Lp-PLA2
Age	30-50	45	3.03	273
	51-70	120	3.10	281
Gender	Female	71	3.05	270
	Male	79	3.12	288
Residence	Urban	73	3.23	281
	Rural	62	3.02	280
	Coastal	15	2.8	273
Type of Occupation	Sedentary	19	3.42	280
	Non-sedentary	131	3.04	276
	Sedentary	19	3.42	280

Distribution of hsCRP and Lp-PLA2 value according to lifestyle and clinical parameters among test subjects was given in table 2. Majority of the test subjects were reported as obese and their observed mean hsCRP and Lp-PLA2 level was higher when compared to those without obesity. Test subjects with habit of smoking and alcohol consumption showed an elevated mean hsCRP and LpPLA2 concentration than the rest. Similarly test subjects reported with History of (H/o) Hypertension, H/o Diabetes mellitus and H/o Dyslipidemia showed higher concentration of both Lp-PLA2 and hsCRP.

Table: 2 Distribution of hsCRP and Lp-PLA2 value according to lifestyle and clinical parameters

Variables	Category	No.	hsCRP	Lp-PLA2
Obesity	Yes	98	3.10	283
	No	52	3.05	279
Smoking	Yes	30	3.12	282
	No	120	3.08	279
Alcohol	Yes	31	3.13	291
	No	119	2.91	277
H/o Hypertension	Yes	58	3.17	281
	No	92	3.04	278
H/o Diabetes Mellitus	Yes	56	3.20	289
	No	94	3.02	264
H/o Dyslipidemia	Yes	79	3.09	284
	No	71	3.08	275

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Distribution of mean hsCRP and Lp-PLA2 level according to lipid profile of test subjects are given in the table 3. Test subjects with high concentration of total cholesterol (>200mg/dL), triglyceride (>150mg/dL) and LDL (>100mg/dL) showed an increased concentration of hsCRP and Lp-PLA2. Test subjects with low concentration of HDL (≤40mg/dL) showed an elevated hsCRP (3.22mg/L) and LpPLA2 (282ng/mL) level.

Table: 3 Distribution of hsCRP and Lp-PLA2 value according to lipid profile:

Variables	Category	No.	hsCRP	Lp-PLA2
Total Cholesterol	≤200	62	2.88	277
	>200	88	3.23	281
Triglyceride	≤150	67	2.90	278
	>150	83	3.23	280
HDL	≤40	98	2.84	282
	>40	52	3.22	275
LDL	≤100	41	2.94	277
	>100	109	3.14	281

Discussion

According to Ghisi et al (2014), persons with CAD often have long - term experience, with chronic conditions, leading to an enormous need for appropriate and correct knowledge regarding the management of diseases. In the current study, 150 individual suffering CAD was selected as test and 100 healthy individuals were included in the control group. Geldsetzer et al (2018) reported that, "a mean CVD risk, which varied from 13.2% in Jharkhand to 19.5% in Kerala". In the present study, test subjects showed an elevated mean hsCRP (3.09±0.99) concentration than the control group (1.75±0.84). Kamath et al (2015) stated that, "analysis of the hsCRP level from the case-control studies derived a mean hsCRP value of 1.88mg/l, which is higher than the western population where values <1 mg/l are classified as low cardiovascular risk".

Sofogianni et al (2018) suggested that, "in both, the population at large and patients with known CAD, increased Lp-PLA2 mass and activities seem to be associated with increased CAD risks". Gregson et al (2012) reported that, "plasma Lp-PLA2 levels may be regarded as an independent biomarker and cardiovascular predictor in primary and secondary prevention". In the current study test subjects showed an increased Lp-PLA2 concentration (280±63.52) than the control group (159±26.06). Vickers et al (2009) pointed out that, "Lp-PLA2 was highly correlated and expressed in plaque rupture areas with greater potential". Thompson et al (2010) found, "a positive relationship between risk of Lp-PLA2 and vascular and non - vascular causes of CAD".

In the Beltrame et al (2012) explained that, "in both females and males, CAD is the leading cause of death, while the initial manifestation of CAD is delayed in women by around ten years compared to men". In the present study it was observed that the hsCRP and Lp-PLA2 concentration was higher in male subjects (3.12mg/L and 288ng/mL) when compare to the female subjects. Lloyd-Jones et al (2010) observed that, "strong effects of ageing on CAD by observing that the risk of CAD increases gradually with age". In the present study also test subjects with advanced age showed an increased mean hsCRP and Lp-PLA2 concentration. Kavi et al (2019) denoted that, "advancing age with lesser education shows an increasing prevalence of CAD risk factors among south Indian population".

Philip and Abraham (2018) pointed out that, "obesity can be the reason for the observed high percentage of incidence and severity of CAD among patients with significant high BMI". In the current study, out 150 test subjects 65.3% (n=98) were reported with obese

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and their observed mean hsCRP and Lp-PLA2 concentration was higher than the rest. According to Centers for Disease Control and Prevention (2012), "obesity was found to be a major risk factor for the development of type-2 diabetes, asthma, hypertension, stroke, osteoarthritis and gynecological complications. In 2012, WHO reported that, "29% of deaths from coronary heart disease can be attributed to tobacco". In the current, it was observed that, test subjects with habit of smoking habit showed an elevated hsCRP and mean Lp-PLA2 level. Iversen et al (2013) suggested that, "smoking and passive smoking have been identified as variable risk factors for acute myocardial infarction and CAD".

In the present study it was observed that, test subjects with alcohol consumption showed an elevated hsCRP (3.13mg/L) and Lp-PLA2 (294ng/mL) level than the rest without habit of alcohol consumption. Bhattad et al (2020) observed in their study that, "2/3rd of patients with CAD with tobacco consumption in any form had hsCRP 1- 3 mg/L". WHO in 2021 reported that, "alcohol consumption is a causal factor in more than 200 disease and injury conditions. Drinking alcohol is associated with a risk of developing health problems such as non-communicable diseases (liver cirrhosis, some cancers and cardiovascular diseases)".

Leon and Maddox (2015) et al reported that, "diabetic patients also have increased amounts of C-reactive protein (CRP), which may contribute to endothelial dysfunction". In the current test subjects reported with H/o DM and dyslipidemia showed an increased hsCRP and Lp-PLA2 concentration than the control subjects. Mohan et al (2010) mentioned that, "both diabetes and impaired glucose tolerance are associated with increased risk of CAD events". Hague et al (2003) denoted that, "hypertriglyceridemia is known in the progression of CAD". Leon and Maddox (2015) et al also estimated that, "the prevalence of HF, particularly heart failure and preserved ejection fraction, is higher in diabetic patients (16%-31%) than the general population (4%-6%)". Dei Cas et al (2015) reported that, "DM may independently alter cardiac structure and function by promoting hypertrophy and fibrosis".

Baloch et al (2014) mentioned that, 'increased serum cholesterol levels are associated with the risk of CAD and decreased levels of low density lipoprotein (LDL) and high density lipoprotein (HDL) are important in the progression of CAD". In the present study test subjects with high level of triglyceride, total cholesterol and LDL showed an increased concentration of Lp-PLA2 and hsCRP. Simon et al (2010) found that, "subjects with CAD had higher TC, LDL and TG values with a low level of HDL". Baloch et al (2014) reported that, "dyslipoproteinemia with high levels of total cholesterol and LDL and low levels of HDL and family history of early CAD have been demonstrated to be predisposing factors of early CAD". It was observed in the present that, test subjects with low level of HDL (≤40mg/dL) showed an elevated mean hsCRP (2.84mg/L) and Lp-PLA2 levels (282ng/mL).

Conclusion

In India the incidence of CAD is rapidly increasing, when compared to other countries. In this scenario, the understanding of various crucial risk factors is critical for the prevention of CAD morbidities and mortality. There are several conventional markers which were used for the early prediction of CAD, but emerging risk markers are also required. In the current study among individuals with CAD showed an elevated Lp-PLA2 and hsCRP concentration. So that, emerging risk markers like hsCRP and Lp-PLA2 provide specific diagnostic and prognostic values when compared to traditional markers.

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