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Comparative study of serum lipid, Lp (a) and hsCRP among the patients with CAD and healthy individuals

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Abstract

Background: Coronary artery Disease (CAD) is one of the most common types of cardiovascular disease with acute myocardial infarction being its most important consequence, hence making it one of the leading causes of death worldwide. CAD is now known to be an active process of cell activation, inflammation and thrombosis which is exacerbated by dyslipidemia. Inflammatory marker- High sensitivity C Reactive protein (hs-CRP) and Lipoprotein (a) are proven to be independent risk predictors of future cardiovascular events.

Aim and objectives: The aim of this study is to compare the lipid profile parameters, Lipoprotein (a) levels and hsCRP between the healthy controls and CAD patients. Also, to study the correlation of hsCRP and Lp(a) with lipid profile parameters (Total cholesterol, Triglycerides, HDL and LDL) and Lp(a)/hsCRP in the CAD group. Additionally, to analyze if there is any significant role of family history in the hsCRP and Lp(a) levels of both; healthy controls and CAD patients.

Materials and Methods: Total cholesterol, triglycerides and high density lipoprotein cholesterols were measured by the auto-analyzer using kits based on enzymatic methods. Low density lipoprotein cholesterol was calculated using the Friedewald's formula. hsCRP and Lp (a) were measured using turbidimetric assays. The obtained data were statistically analyzed by SPSS 16.

Results: There was significant difference in the Lipid profile parameters, hsCRP and Lp (a)

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between the control and CAD. HsCRP was correlated with the other study parameters. Significant correlation of hsCRP was observed with Lipid profile parameters and with Lp (a), the correlation was found to be insignificant. Also, significant correlation of Lp (a) was observed with lipid profile parameters except HDL and with hsCRP and HDL, the correlation was found to be insignificant. A family history of CAD had significant influence on both, hsCRP and Lp (a) levels in the CAD group. However family history did not have a significant influence on Lp(a) levels in the healthy control group.

Conclusion: The 3 major biochemical analytes of CAD i.e. lipid profile, hsCRP and Lp (a) along with the presence of a family history of CAD are independent risk factors for the development of CAD. Young adults with presence of co-morbidites like obesity, dyslipidemia, hypertension should also be periodically checked for hsCRP and Lp(a) levels along with the other biochemical parameters to keep the development of CAD in check.

Key word: Coronary artery disease, Lp(a), hsCRP, family history

Introduction

Coronary artery Disease (CAD) is one of the most common types of cardiovascular disease. Acute myocardial infarction is the most important consequence of CAD, making it one of the leading causes of death worldwide [1]. A study by Global burden of Disease has stated that age –standardized CVD death rate in India is 272 per 100000, which is substantially higher that the global average of 235 [2]. To be precise, the prevalence of CAD in India is 21.4 % for individuals living with Diabetes mellitus and 11% for non-diabetics. Also, the prevalence in urban population is double to that of rural population [3]. The conventional risk factors for the development of CAD include- Type 2 Diabetes mellitus, hypertension, dyslipidemia, smoking, obesity, sedentary lifestyle, low fiber intake and psychosocial stress [4-7].

CAD results due to buildup of cholesterol as plaques in the coronary arteries, which results in reduced blood flow and in turn decreased oxygen supply to the heart. This phenomenon is called as atherosclerosis, which is now known to be an active process of cell activation, inflammation and thrombosis [8]. This inflammatory process is explained to be exacerbated by the other cardiovascular risk factors like dyslipidemia with special reference to elevated Low density lipoprotein (LDL) cholesterol and decreased High density lipoprotein (HDL) cholesterol levels [9].

Many large clinical trials have shown that inflammatory biomarker- high sensitivity C Reactive protein (hs-crp) is an independent risk predictor of future cardiovascular events. Some studies have concluded that the addition of hs-crp to the earlier mentioned risk factors acts an independent significant predictor unit of cardiometabolic risk [10].

Lipoprotein (a) – Lp (a) is another significant risk factor for CVD. It is composed of Low density lipoprotein (LDL) cholesterol like particle bound with cringle shaped glycoprotein i.e. apolipoprotein –apo (a). In patients with established CAD, high Lp (a) levels are associated with increased cardiovascular risk [11]. This present study brings together the 3 major biochemical risk analytes of CAD i.e. lipid profile, hscrp and Lp (a) which are studied in both

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CAD patients and age matched healthy controls.

The aim of this study is to compare the lipid profile parameters, Lipoprotein (a) levels and hsCRP between the healthy controls and CAD patients. Also, to study the correlation of hsCRP and Lp(a) with lipid profile parameters (Total cholesterol, Triglycerides, HDL and LDL) and Lp(a)/hsCRP in the CAD group. Additionally, to analyze if there is any significant role of family history in the hsCRP and Lp(a) levels of both; healthy controls and CAD patients.

Materials and methods

The present study was carried out in the Department of Biochemistry, Yenepoya medical college- Mangalore, Karnataka. The duration of the study was for a period of 1 year i.e. from June 2019 to June 2020. The Institutional Ethics committee gave permission to carry out the study. Written informed consent was obtained from each participant of the study. The study comprised of 200 participants between the ages of 18 and 80 years. The participants included 100 CAD patients with a history of angina and 100 age-matched healthy controls. Individuals with acute or chronic renal diseases, thyroid disorders, acute infections, recent stroke, diabetic ketoacidosis, non-ketotic hyperosmolar diabetes and any recent surgery in the last three months were excluded from the study.

Two milliliters of venous blood sample was collected after at least 8 hr of fasting. Total cholesterol, triglycerides and high density lipoprotein cholesterols were measured by the auto-analyzer using kits based on enzymatic methods. Low density lipoprotein cholesterol was calculated using the Friede-wald formula. LDL Cholesterol = Total Cholesterol - (TGL/5 + HDL). hsCRP and Lp (a) were measured using turbidimetric assays. The obtained data were statistically analyzed by SPSS 16.

Result

The comparative analysis among the control group and the study group (Coronary artery disease/CAD patients) with respect to age, BMI (body mass index) and WHR (waist hip ratio) are shown in figures 1, 2 and 3 respectively. Significant differences in mean values were observed in case of BMI and WHR. The study group had significantly high BMI and WHR ($p<0.05$).

In table 1 comparison was made with respect to lipid parameters and hs- CRP. The study group (CAD group) had significantly high levels of total cholesterol (TC), triglycerides (TG), LDL, lipoprotein a or Lp (a) and hs CRP while the level of HDL was significantly low ($p<0.05$).

Hs-CRP was correlated with the other study parameters. Significant correlation was observed with TC, TG and LDL. The correlation of hs-CRP with RG, TG and LDL was positive and with HDL it was negative. Hs-CRP though correlated positively with Lp (a), it was insignificant ($p>0.05$, table 3).

In table 4, correlation of Lp (a) with other study parameters is elucidated. Lp (a) correlated significantly with TC, TG and LDL. The correlation was positive. The correlation of Lp (a)

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with HDL and hs-CRP was insignificant (p>0.05).

The influence of family history of CAD on the levels of CRP and Lp (a) is demonstrated in table 5. In case of control group significantly high levels of CRP was observed in the patients having positive family history of CAD. However, there was no significant difference in the level of Lp (a) when comparison was made between patients with and without family history of CAD. Likewise in case of patient group, both hs-CRP and Lp (a) levels were significantly high in the patients with positive family history of CAD compared to those without positive family history (p<0.05).

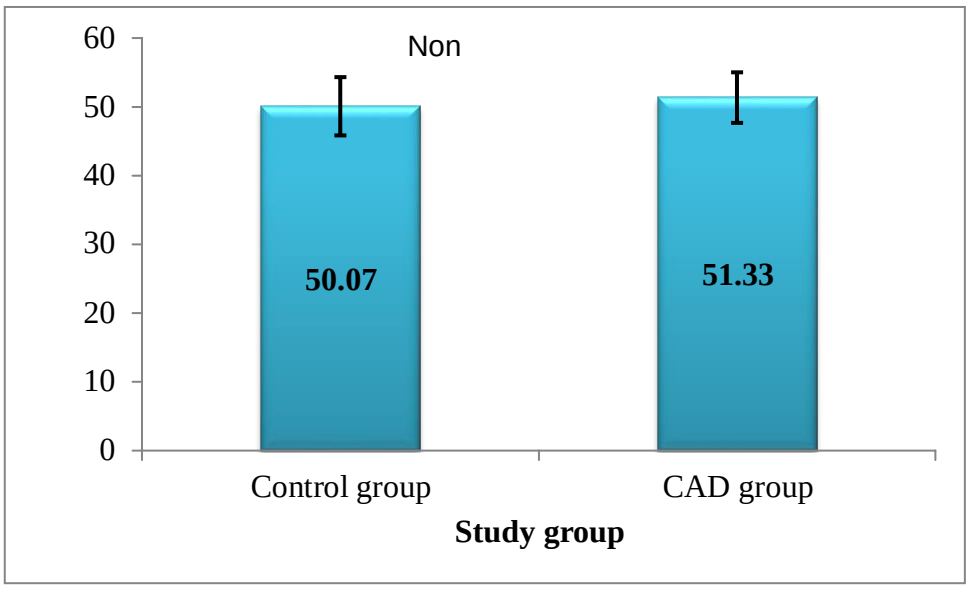

Figure 1: Comparison of age in control and patient groups

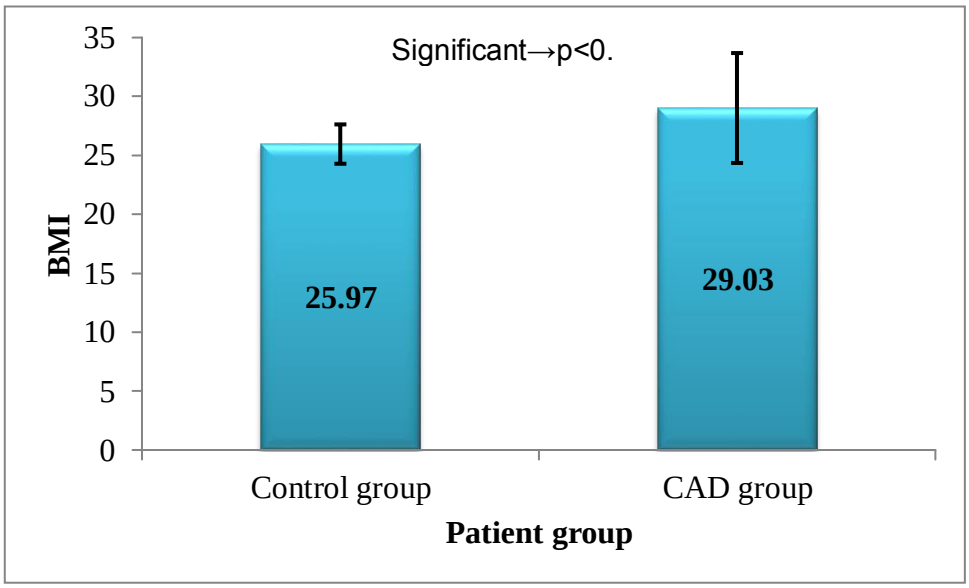

Figure 2: Comparison of BMI (Body mass index) in control and patient groups

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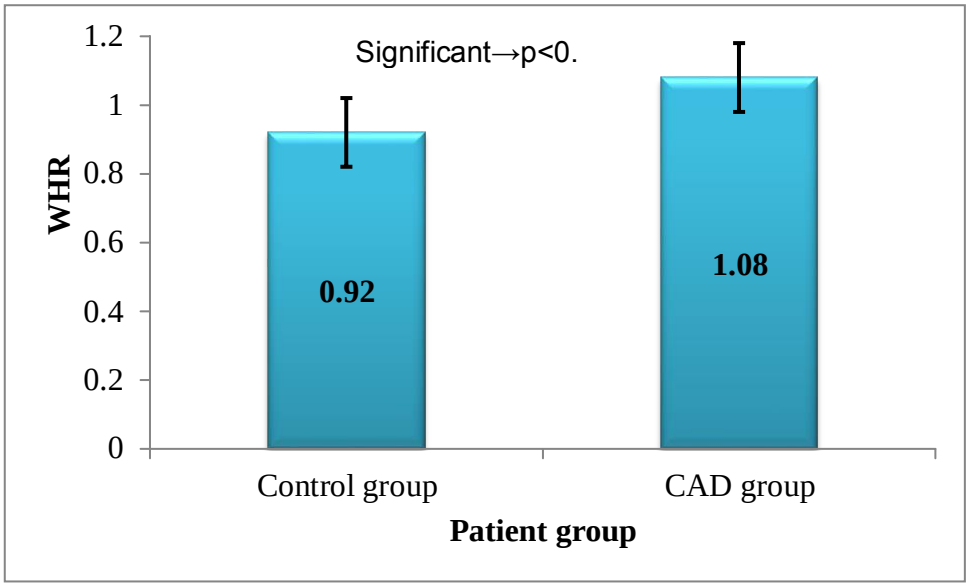

Figure 3: Comparison of WHR (Waist-hip ratio) in control and patient groups

Table 1: Comparison of biochemical parameters among control group and CAD group

Parameters	Control group	CAD group	p
Total cholesterol (mg/dL)	165.93±25.3	209.52±40.17	<0.05
HDL (mg/dL)	46.15±4.03	34.14±3.46	<0.05
Triglyceride (mg/dL)	105.21±20.68	169.2±27.02	<0.05
LDL (mg/dL)	97.54±16.91	139.65±24.29	<0.05
CRP (mg/L)	1.86±0.42	5.76±1.38	<0.05
LP a (mg/dL)	28.03±4.8	57.17±7.95	<0.05

Table 2: Correlation of CRP with the biochemical parameters

Parameters	r	p
Total cholesterol	0.59*	<0.05
HDL	-0.61*	<0.05
Triglyceride	0.65*	<0.05
LDL	0.41*	<0.05
Lp (a)	0.032	>0.05

Table 3: Correlation of Lp (a) with the biochemical parameters

Parameters	r	P
Total cholesterol	0.63*	<0.05
HDL	0.2	>0.05
Triglyceride	0.55*	<0.05
LDL	0.38*	<0.05
CRP	0.032	>0.05

Table 4: Lp (a) and CRP levels based on family history

Study group	Family history	Number	Lp (a)	CRP

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Control group	Present	23	29.32±3.62	2.66±0.44
	Absent	77	27.41±2.99	1.15±0.32
p			>0.05	<0.05
CAD group	Present	68	67.21±7.39	6.55±2.05
	Absent	32	48.15±5.55	4.71±1.18
p			<0.05	<0.05

Discussion

In developed countries coronary artery disease is the major cause of morbidity and mortality. Recent trends show the rapid surge of development of premature CAD among young individuals. Besides the morbidity and mortality risks, CAD also causes economic burden to the patients. Premature CAD has several predisposing factors such as obesity or physical inactivity, family history, smoking, homocysteinemia, familial hypercholesterolemia, mental stress and depression [12].

Dyslipidemia is characterised by low HDL, and high TC, TG and LDL. Of these, LDL is the most potent one to induce atherogenesis because coronary events can occur even in the individuals with the level of LDL below 130 mg/dL. It is the level generally considered to be average in the individual with no overt CAD [13]. In this study, significantly high levels of TC and TG; and significantly low HDL were observed in patients with CAD compared to control group.

Hence the diagnosis of subclinical coronary events have become the priority issues to strictly consider in recent decades. Various markers that can improve diagnosis of atherosclerosis or coronary artery events at subclinical stage have been studied. Some of such markers are CRP and Lp (a). We observed significantly high Lp (a) and hs-CRP in CAD patient group.

Studies have shown inflammation to play significant roles in the atherogenesis and hs-CRP is the independent and promising marker of CAD. Any infection or trauma can cause leukocyte activation and release of Il-6 which further stimulates the production of hs-CRP. Hs-CRP induces atheroscelrosis by activating complement pathway, facilitating monocyte adhesion and recruitment in [14]. In the study of Jager A etal hs-CRP was associated with 2 fold increased risk of cardiovascular mortality after the adjustment of age and sex [15].

Atherosclerotic lesion consists of abundant amount of hs-CRP mRNA and the interventions such as diet, exercise, blood pressure management that are known to decrease onset of cardiovascular events reduced the hsCRP levels [16].

Hs-CRP is a strong predictor of stroke and heart attack compared to LDL. The CVD risk is higher in the individuals with high hs-CRP and low HDL compared to those with low hs-CRP and high LDL [17].

Lp (a) is a modified form of LDL and has significant role in CAD development. It on accumulation in atherosclerotic lesions causes smooth muscle proliferation and suppresses glucocorticoid receptors. Lp a level is increased in CAD and can contribute to restenosis following angioplasty [18]. Previous studies in Indian population have shown that Lp (a) levels significantly increase in among coronary artery disease compared to healthy cases.

Both retrospective and prospective research studies have documented independent association between CAD and Lp (a) in African Americans and Asian Indians. However, in the study of

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Jauhiainen M et al, the baseline levels of Lp (a) were comparable between who developed CAD on the follow up for 5 years and the patients who did not develop [19]. This study suggested that Lp (a) is not an independent risk factor for CHD.

Epidemiological study conducted by Gambhir et al reported Lp (a) to be an independent CAD risk for the patients of age less than 40 years [20]. Several studies have established a cut off value of Lp (a) for the assessment of CAD risk. In a study conducted in Caucasian population the cut off value of Lp (a) established was 30 mg/dL [21] while a multiethnic study revealed that 30 mg/dL cut off value is applicable for Black population and the cut off value of 50 mg/dL should be taken into account for Caucasian and Hispanic populations [22]. Since the cut off values of Lp (a) varies with the ethnicity race specific cut off values must be established in Indian population too with proper clinical correlation.

In the previous studies the levels of Lp (a) levels were 2 folds higher in Indians as compared to Malays, Caucasians and Chinese residents in Singapore [23]. Similarly in the CADI study conducted on the Immigrant Indian population higher Lp (a) were found in Asian Indians as compared to whites thus suggesting Indians to be at higher risk for CAD [24]. A study was conducted in North Indian population by Ashfaq F etal. They showed the concentration of Lp (a) to be 18.9 mg/dL in the patients with normal coronary artery while the levels were 39.2 mg/dL, 58 mg/dL and 69.2 mg/dL for Grade I vessel, garde II vessel and Grade III vessel respectively [25].

Lp (a) when present in higher concentration also augments the apolipoprotein and total cholesterol associated risks. Elevated levels of Lp (a) also supercedes the benifical effects of HDL cholesterol though they are not related directly to one another.

Ridker PM *et al* in their study tried to demonstrate the association between the levels of hs-CRP and LDL after statin with recurrence of coronary artery events. They found that in the patients with low hs-CRP levels following statin therapy showed better clinical output compared to those with high hs-CRP levels. It was independent of the level of LDL [26]. Therefore it is suggested to monitor both hs-CRP and cholesterol level while following the strategies to reduce cardiovascular risks using statin therapy.

Hs-CRP and Lp(a) were correlated with lipid profile parameters. Lp (a) correlated significantly and positively with TC, LDL and TG while CRP correlated significantly and positively with TC, LDL and TG; and significantly and negatively with HDL. The correlation of Lp (a) with hs-CRP was insignificant. The pathogenicity of Lp (a) is influenced by the levels of other serum lipids too. Several investigators reported correlation between Lp(a) and other lipid variables. In the present study a significant correlation was observed between HDL and LDL cholesterol levels and Lp (a). This observation was compatible with study from Beena G *et al* [27].

Lipoprotein(a) significantly correlated positively with TC and LDL in the study of Rafi A *et al* [28]. Total Cholesterol and LDL-Cholesterol have a tendency to have high Lp(a) levels , as shown in the study by Shen Y et al [29]. In the present study it was observed that the levels of Lp (a) and hs-CRP were significantly high in the CAD patients with positive family history compared to those CAD patients without the family history. In case of control group significantly high levels of hs-CRP was obtained in the control with positive family history than the controls without the family history of CAD. As per Goel PK *et al* second most common

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risk factor of premature CAD in young Indian was the family history of CAD [30] Therefore there is need of analysis of genetic factors responsible for atherogenesis or coronary artery events and lipid metabolism. Lp (a) is one of the potential agent that facilitate premature CAD development in Indians. Lp (a) holds a strong genetic predisposition suggesting the future generation of affected individuals to be at increased risk of developing CAD.

Conclusion

CAD patients are dyslipidemic and have higher levels of Lp (a) and hsCRP compared to normal individuals. Hence new therapeutic approaches should be developed to lower Lp(a) levels, along with hs-CRP; that can be fruitful in the patients with CAD. It may also be useful in reducing the risk of CAD especially among those individuals with the positive family history of CAD.

Conflict of interest: Nill

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