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Circulating PCSK9 levels and conventional risk factors in CAD

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ABSTRACT

Coronary artery disease (CAD) is the chief cause of mortality and morbidity worldwide. The aim of this study was to compare the levels PCSK9 and conventional risk factors of CAD in CAD patients and age and sex-matched controls and also to evaluate the relationship of circulating PCSK9 levels with other conventional risk factors of coronary artery patients. Sixty two clinically proved CAD patients and sixty-two healthy; age and sex-matched subjects without CAD were selected for the study. Detailed clinical and other relevant data were recorded using proforma. Five ml of fasting venous blood was collected from all the subjects and used for the investigations of fasting plasma glucose (FPG), HBA1C, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol (Direct), Apo B and PCSK9. The outcomes of this study showed that levels of FPG, HbA1c, lipid parameters-total cholesterol, triglycerides, LDL-c, Apo B were significantly higher whereas HDL-c were significantly low in CAD patients compared to normal controls. Circulating PCSK9 level was significantly elevated, and its level was correlated with other risk parameters. This study found that circulating PCSK9 level was significantly high, and its level was correlated with other risk parameters.

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INTRODUCTION

Coronary Artery Disease (CAD) is the single largest cause of death in developed countries and is one of the principal causes of disease burden in developing countries as well. In the past two decades, there has been an alarming increase in the prevalence of CAD and cardiovascular mortality many South Asian countries including India. The burgeoning burden of CAD in India due to the increase in the predominance of coronary risk factors such as diabetes, hypertension, atherogenic dyslipidemia, smoking, central obesity and physical inactivity (Krishnan, 2012). Several traditional risk factors for CAD are linked to lifestyle, and preventative strategy can be tailored to altering particular determinants. Novel risk factors also may leads to CAD (Mack and Gopal, 2016).

Lipids perform a significant role in the development of atherosclerosis (Calder, 2012). Hyperlipidemia is a well-established risk factor for developing cardiovascular disease (CVD) (Chaudhary *et al.*, 2017). Increasing of blood cholesterol (mainly LDL) promotes disease. Increased Low density lipoprotein-Cholesterol (LDL-C) is an important risk factor for cardiovascular disease (Delles *et al.*, 2003). The high-density lipoprotein cholesterol (HDL-C) is regarded as anti-atherogenic good cholesterol. It is linked in the reverse transport of lipids. Triglyc-

erides increase the risk of CAD by increasing the LDL level, decreasing HDL level, disrupting the function of artery walls, and activating the thrombogenic factors and plasminogen activators (Harchaoui *et al.*, 2009). Extensive investigations clearly have shown the lipid-lowering effect in primary and secondary prevention of CAD (Riwanto *et al.*, 2013).

LDL-cholesterol has been the target of therapy for improving outcomes in patients at high risk for developing CVD (Stone *et al.*, 2014). Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) is a hepatic protease that attaches to and internalizes Low-density lipoprotein-Cholesterol receptor [LDLR] into lysosomes hence promoting their destruction (Lambert *et al.*, 2012). PCSK9 regulates LDLR degradation and could potentially be a target for modulating LDLR expression and consequently, LDL-C levels (Seidah *et al.*, 2003; Abifadel *et al.*, 2003). By preventing LDL receptor destruction, LDL-C levels can be lowered 50%-60% above that achieved by statin therapy alone (Chaudhary *et al.*, 2017). On the other hand, elimination of function mutations and treatment with PCSK9 inhibitors are consistently connected with a lower risk of cardiovascular situations, chiefly associated to relevantly decrease circulating LDL cholesterol. PCSK9 inhibitors target and inactivate proprotein convertase subtilsin-kexin type 9 (PCSK9), a hepatic protease that attaches and internalizes LDL receptors into lysosomes hence promoting their destruction.

This chief objective of this study was to assess the relationship of circulating PCSK9 levels with other conventional risk factors of coronary artery patients. This study also aimed to compare the levels of PCSK9 and conventional risk factors of CAD in CAD patients and age and sex-matched controls.

MATERIALS AND METHODS

Sixty two clinically proved CAD patients referred from the Out-Patient Department of Saveetha Medical College, Thandalam, Chennai were selected for the study. Sixty-two healthy, age and sex-matched subjects without CAD formed the control group. Detailed clinical and other relevant data were recorded using proforma. Five ml of fasting venous blood was obtained from all the subjects, and the following investigations were performed.

Fasting plasma glucose (FPG), HbA1C, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol (Direct) and Apo B were estimated in fully automatic chemistry analyzer. PCSK9 levels were estimated using a commercially available ELISA kit (Human Diagnostics, Germany)

Statistical Analysis: T-test was done to compare the PCSK9 levels and conventional risk factors like FPG, HBA1C, TC, TG, HDL cholesterol and LDL cholesterol (Direct) between patients and controls. The level of statistical significance was made with a p-value of <0.05. Pearson correlation was used to find out the correlation between PCSK9 levels with other conventional risk factors.

RESULTS

In the present study, 62 clinically proven CAD subjects and 62 normal control subjects were included. All subjects were taken within the age group of 30 to 75 years. Regarding the age, the test group's age ranged from 30 to 71, with a mean age of 51.9. The observed mean age of the control subjects was 47.43 (age ranged from 35-75). The majority (75.0%) of the study subjects were males. In control subjects, 66.1% were males.

High levels of FPG and HbA1c observed among CAD patients compared to control subjects (Table 1) which were statistically significant.

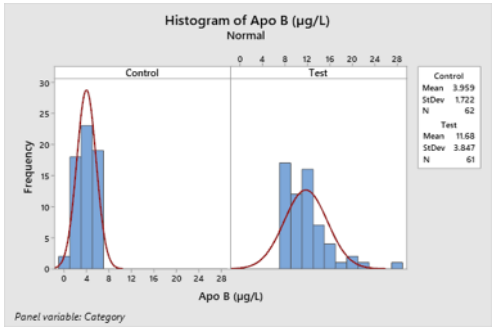

Figure 1: Apo B levels of study subjects and controls subjects

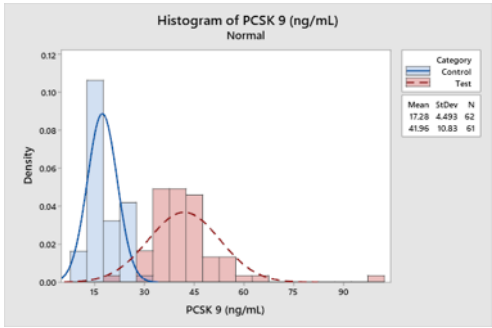

Figure 2: Histogram of PCSK 9

The levels of TC, TG, HDL cholesterol, low-density lipoprotein (LDL) cholesterol (Direct) were compared and shown in Table 2.

The levels of Apo B were compared among the subjects and shown in Figure 1.

PCSK9 level showed a statistically significant

Table 1: FPG and HbA1c levels of study subjects and controls subjects

Risk factor	CAD	Control	T value	P
FPG	139.1±52.3	90.3±5.5	-7.24	<0.01
HbA1c	5.66±1.08	4.75±0.39	-6.21	<0.01

Table 2: Lipid profile levels of study subjects and controls subjects

Risk factor	CAD	Control	T Value	P
TC [mg/dl]	229.8±27.4	176.9±13.8	-13.6	<0.01
TG [mg/dl]	173.6±26.96	120.0±19.95	-12.52	<0.01
HDL [mg/dl]	36.3±2.83	47.65±4.69	16.27	<0.01
LDL [mg/dl]	157.5±24.9	110.7±10.6	-13.52	<0.01

Table 3: PCSK9 levels of study subjects and controls subjects

Risk factor	CAD	Control	T Value	P
PCSK9 [ng/ml]	41.96±10.83	17.28±4.49	-16.46	<0.01

Table 4: Correlation of PCSK9 levels with other conventional risk factors

	r value	P-Value
FPG	0.361	<0.01
TC	0.670	<0.01
TG	0.630	<0.01
HDL	-0.660	<0.01
LDL	0.644	<0.01

increase among the study subjects than the control subjects and is given in Table 3 and Figure 2.

Correlation study of PCSK9 levels with other conventional risk factors was carried out, and the results were shown below (Table 4).

DISCUSSION

In this study, we compared the levels of circulating PCSK9 concentration and other risk factors such as FPG, HbAIc, and lipid profile in a group of normal healthy subjects and CAD patients. The outcomes of the instant study reported that levels of PCSK9, FPG, HbA1c, lipid parameters -total cholesterol, triglycerides, LDL- c, Apo B were significantly higher whereas HDL- c were significantly low in CAD patients compared to normal controls. Circulating PCSK9 level was significantly correlated with other risk parameters.

Coronary artery disease (CAD) is frequently associated with glucose disturbances. Many studies have investigated the influence of abnormal glucose homeostasis on the risk of subclinical atherosclerosis or CVD (Moebus *et al.*, 2009). HbA1c is an important pointer of long-term glycemic control with the ability to reveal the combined glycemic history of the leading two to three months. HbA1c not only gives a reliable test of chronic hyperglycemia but also correlates strongly with the risk of long-term diabetes complications. According to Sherwani *et al.* (2016), elevated HbA1c has also been regarded as an independent risk factor for coronary heart disease also stroke in subjects with or without diabetes. The valuable information provided by a single HbA1c test has rendered it as a reliable biomarker for the diagnosis and prognosis of diabetes. Our results are well agreement with the above studies as we have high FPG, HbA1c values in CAD patients.

Guidelines for the control of patients with dyslipidemia primarily concentrate on accomplishment of goal low-density lipoprotein cholesterol (LDL-C) levels for coronary heart disease (CHD) risk decrease (NCEP-ATP III) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). It is well-established that a low quantity of HDL-C is associated with a raised risk of CHD and increasing concentrations are associated with a reduction in risk of CHD (Desforges *et al.*, 1989). Epidemiological studies have observed inverse connection of HDL-C and coronary heart dis-

ease (CHD) risks (Rajagopal *et al.*, 2012). There is rising attention in high-density lipoprotein cholesterol (HDL-C) as a second line target of therapy. APO B directly reflects the number of plasma atherogenic lipoproteins since each particle of LDL, IDL, and VLDL involves just one APO B (Mashayekhi *et al.*, 2014).

Many studies reported that PCSK9 plasma levels were connected with the cruelty of coronary injuries in patients amongst acute coronary syndrome and myocardial infarction (Pott *et al.*, 2018; Cariou *et al.*, 2017; Bae *et al.*, 2018).

Similarly, most studies investigating the association between plasma PCSK9 and early coronary atherosclerosis described a not clear direct relationship (Nose *et al.*, 2019). A study by Caselli *et al.* (2019) demonstrated higher levels of circulating PCSK9, being related to moderately higher levels of total and LDL cholesterol.

In the present study, we observed that circulating PCSK9 level was correlated with other risk parameters such as FPG, HbA1c, lipid parameters -total cholesterol, triglycerides, LDL- c, HDL-C and Apo B. Many previous studies have similar observations. Lipid parameters and statin treatment have the highest relationship with PCSK9 levels in patients without renal dysfunction (Sahebkar *et al.*, 2015; Kim *et al.*, 2016).

Circulating PCSK9 level was separately correlated with serum glucose, albumin, total cholesterol level, and statin treatment. Higher circulating PCSK9 level was separately associated with a more elevated chance of composites of cardiovascular event and death in hemodialysis (HD) patients (Hwang *et al.*, 2020).

It has been identified that PCSK9 levels have correlations typically with other atherogenic risk factors positively, such as plasma triglyceride (TG), blood pressure, body mass index (BMI), fasting plasma glucose, insulin levels, white blood cell count, C-reactive protein levels and smoking (Chernogubova *et al.*, 2012; Cui *et al.*, 2010; Li *et al.*, 2014).

CONCLUSION

In the present study, we observed that circulating PCSK9 level was significantly high in CAD patients compared to normal controls. Other risk factors [FPG, HbA1c, lipid parameters -total cholesterol, triglycerides, LDL- c, Apo B] were also high, whereas HDL- c was significantly low in CAD patients. We also observed a significant correlation between circulating PCSK9 concentration and other risk factors.

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Conflict of interest

There is no conflict of interest among authors.

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