Section: Biochemistry

Original Research Article

# SERUM PROPROTEIN CONVERTASE SUBTILISIN/KEXIN 9 AND THEIR RELATIONSHIP WITH TRADITIONAL CARDIOVASCULAR RISK FACTORS IN CAD

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ABSTRACT

**Background:** Coronary Artery disease (CAD) is the leading cause of mortality in the developed nations and also represents a major contributor to disease burden in developing countries. loss of function mutations and treatment with PCSK9 inhibitors are consistently associated with lower risk of cardiovascular events, mainly attributed 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.

**Materials and Methods:** Sixty two clinically proved CAD patients referred from Out Patient Department of P K Das Institute of Medical Sciences , Vaniamkulum, Ottapalam,Palakkad were selected for the study. 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 commercially available ELISA kit [Human Diagnostics, Germany]

**Results:** A high levels of FPG and HbA1c observed among CAD patients when compare to control subjects which was statistically significant. PCSK9 level showed a statistically significant increase among the study subjects than the control subjects.

**Conclusion:** 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. We found that circulating PCSK9 level and other risk factors [FPG, HbA1c, lipid parameters -total cholesterol, triglycerides, LDL- c, Apo B] were high in CAD patients. We found a significant correlation between circulating PCSK9 concentration and other risk factors.

**Keywords:** Coronary artery disease, PCSK9. Cardiovascular risk factors, Dyslipidemia, Serum biomarkers.

## INTRODUCTION

Coronary Artery disease (CAD) is the leading cause of mortality in the developed nations and also represents a major contributor to disease burden in developing countries. Over the last two decades the prevalence of CAD and cardiovascular related deaths has increased significantly in India and other south Asian countries. The growing burden of CAD in India can be explained by the alarming rise in the prevalence of coronary risk factors like diabetes, hypertension, atherogenic dyslipidemia, smoking, central obesity and physical inactivity.[1] Several conventional risk factors for CAD are related to lifestyle, and preventative treatment can be tailored to modifying specific factors. Novel risk factors also may contribute to CAD.[2] Hyperlipidemia is a well-established risk factor for developing cardiovascular disease.[3] Low density lipoprotein-Cholesterol [LDL-C] has been the target of therapy for improving

outcomes in patients at high risk for developing CVD [Stone2014]. Proprotein convertase subtilisin/kexin type 9 (PCSK9), has been recently identified as a new target for LDL lowering treatments. 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 2012]. PCSK9 regulates LDLR degradation and could potentially be a target for modulating LDLR expression and consequently LDL-C levels.[3,4] Gain of function mutations of PCSK9 are associated with high plasma LDL cholesterol levels and increased risk of cardiovascular events. By preventing LDL receptor destruction, LDL-C levels can be lowered 50%-60% above that achieved by statin therapy alone.[5] On the other hand, loss of function mutations and treatment with PCSK9 inhibitors are consistently associated with lower risk of cardiovascular events, mainly attributed 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. By preventing LDL receptor destruction, LDL-C levels can be lowered 50%-60% above that achieved by statin therapy alone.[6] The main purpose of the present study was to compare the levels PCSK9 and conventional risk factors of CAD in CAD patients and age and sex matched controls. This study was also aim to evaluate the relationship of circulating PCSK9 levels with other conventional risk factors of coronary artery patients.

**Aim and objective:** The main purpose of the present study was to compare the levels PCSK9 and conventional risk factors of CAD in CAD patients and age and sex matched controls. This study was also aim to evaluate the relationship of circulating PCSK9 levels with other conventional risk factors of coronary artery patients.

## MATERIALS AND METHODS

Sixty two clinically proved CAD patients referred from Out Patient Department of P K Das Institute of Medical Sciences, Vaniamkulum, Ottapalam, Palakkad 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. Four ml of fasting venous blood was collected 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 commercially available ELISA kit [Human Diagnostics, Germany], The study protocol was approved by the institutional human ethics committee of the institute (IEC NO-EC/AS/05/19)

**Statistical Analysis:** Ttest 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.

**Ethical considerations:** The study protocol was approved by the institutional human ethics committee (IEC-NO/EC/AS/05/19).

## 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). Majority (75.0%) of the study subjects were males. In control subjects 66.1% were males. A high levels of FPG and HbA1c observed among CAD patients when compare to control subjects (Table – 1) which was 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 |

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

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

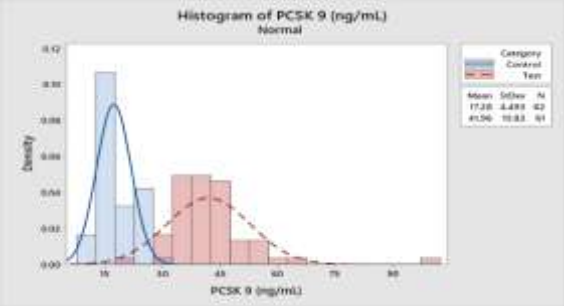
| Risk factor | CAD | CONTROL | T VALUE | P |
|---|---|---|---|---|
| TC [mg/dl] | 228.8±26.9 | 176.9±13.8 | -13.6 | <0.01 |
| TG [mg/dl] | 173.6±26.96 | 120.0±19.95 | -12.52 | <0.01 |
| HDL [mg/dl] | 36.3±2.83 | 47.65±4.69 | 16.27 | <0.01 |

| | | | | |
|---|---|---|---|---|
| LDL [mg/dl] | 157.5±24.9 | 110.7±10.6 | -13.52 | <0.01 |
| Apo B [microgram/L] | 11.68±3.85 | 3.96±1.72 | -14.33 | <0.01 |

PCSK9 level showed a statistically significant increase among the study subjects than the control subjects and is given in table 3 and fig.1

**Table 3: PCSK9 levels of study subjects and controls subjects**

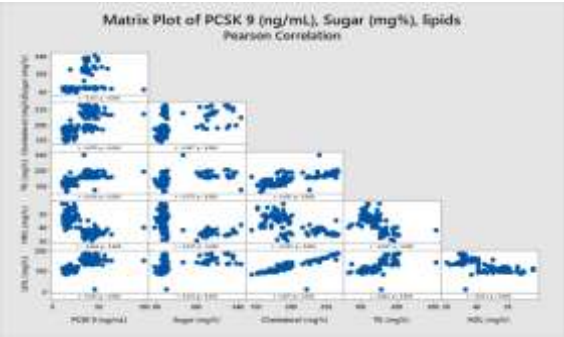
| Risk factor | CAD | CONTROL | T VALUE | P |
|---|---|---|---|---|
| PCSK9 [ng/ml] | 41.96±10.83 | 17.28±4.49 | -16.46 | <0.01 |




Correlation study of PCSK9 levels with other conventional risk factors were carried out and the results were shown below.

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

| | r value | P Value |
|---|---|---|
| FPG | 0.362 | <0.01 |
| TC | 0.669 | <0.01 |
| TG | 0.630 | <0.01 |
| HDL | -0.648 | <0.01 |
| LDL | 0.651 | <0.01 |




## DISCUSSION

The results of the present 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 high and its level was 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.[7-9] HbA1c is an important indicator of long-term glycemic control with the ability to reflect the cumulative glycemic history of the preceding two to three months. HbA1c not only provides a reliable measure of chronic hyperglycemia but also correlates well with the risk of long-term diabetes complications. Elevated HbA1c has also been regarded as an independent risk factor for coronary heart disease and stroke in subjects with or without diabetes.[10-11] 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. Lipid parameters also have an important role in CAD. In the Multi-Ethnic Study of Atherosclerosis (MESA), triglycerides, LDL cholesterol and HDL cholesterol were associated with a risk of incident coronary artery calcification [CAC].[12]

[2016] high levels of LDL cholesterol (LDL-C) and triglycerides and low levels of HDL cholesterol (HDL-C) are associated with an increased risk of cardiovascular events. APO B directly reflects the number of plasma atherogenic lipoproteins since each particle of LDL, IDL, and VLDL involves just one APO B.[13]

Many studies reported that PCSK9 plasma levels were associated with the severity of coronary lesions in patients with acute coronary syndrome and myocardial infarction.[14] Similarly, most studies exploring the association between plasma PCSK9 and early coronary atherosclerosis demonstrated a not clear direct relationship.[15]

Lipid parameters and statin treatment have excellent correlation with PCSK9 levels in patients without renal dysfunction.[16] Circulating PCSK9 level was independently correlated with serum glucose, albumin, total cholesterol level, and statin treatment.

Higher circulating PCSK9 level was independently associated with greater risk of composites of CV event and death in HD patients which is in agreement with our study.

## CONCLUSION

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. We found that circulating PCSK9 level and other risk factors [FPG, HbA1c, lipid parameters -total cholesterol, triglycerides, LDL- c, Apo B] were high in CAD patients. We found a significant correlation between circulating PCSK9 concentration and other risk factors.

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