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Association between plasma homocysteine levels and coronary artery disease

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Abstract

Objectives: Various studies have proposed that increased plasma homocysteine level causes both venous and arterial thrombosis contributing to myocardial Infarction, stroke, and pulmonary embolism, though the results are still debatable. In addition, the homocysteine levels show a genetic and ethnic predisposition. The present study thus aimed to evaluate the association between plasma homocysteine levels and coronary artery disease in Indian patients.

Material and Methods: The present study was a hospital-based case-control study, conducted at a tertiary care hospital in North India. The study included 237 diagnosed cases of acute coronary syndrome (ACS) who were compared with 50 age and sex matched apparently healthy controls. Subjects of the two groups were compared for levels of plasma homocysteine, lipid profile and other conventional risk factors of coronary artery disease (CAD). Homocysteine levels were analysed by chemilumniscence immunoassay. Statistical analysis was performed using SPSS v.21.0. Values were expressed as a mean ± standard deviation or as percentages. Student's t test and Chi square test was used to evaluate statistical significance.

Result: The mean homocysteine levels were found to be significantly higher ($p<0.001$) in patients of ACS as compared to the healthy controls (14.34 ± 7.49 µmol/L and 11.34 ± 4.91µmol/L respectively). However, no association was found between homocysteine level and the conventional risk factors.

Conclusion: The results suggest that high levels of homocysteine are associated with ACS and may be used for risk assessment of CAD. However, further studies with larger sample size would be required to validate the findings.

Keywords: Coronary Artery Disease, Homocysteine, Risk factors.

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1. Introduction

Coronary artery disease (CAD) is globally regarded as one of the leading causes of mortality and morbidity both in the developed and the developing countries.[1] Worldwide, CAD is said to affect around 126 million individuals which is around 1.72% of the total world population.[2] The prevalence of the disease in the Indian population is on the rise and in the last 60 years it has been found to increase alarmingly from 1% to 10% in urban population and 1 to 1-4% in rural population.[3]

The major risk factor for CAD as outlined by the Framingham heart study are older age, smoking, hypertension, diabetes mellitus, high plasma low-density lipoprotein (LDL) land low plasma high-density lipoprotein (HDL), obesity and physical inactivity.[4] Inspite of a wide range of established risk factors of CAD, the incidence of the disease is on the rise. So, a need is continuously felt for establishing newer risk factors for early diagnosis of CAD. The recently investigated newer risk factors include especially homocysteine and lipoprotein (a).

Homocysteine is a sulfur containing amino acid produced by demethylation of essential amino acid methionine as product of numerous transmethylation reactions.[5] Hyper-homocystenemia may arise from the variation of genetic and nutritional deficiency.[6] It causes both venous and arterial thrombosis, contributing to stroke, myocardial infarction and pulmonary embolism.[7] The exact mechanism of homocysteine induced endothelial injury is still not established but it has been suggested that the increased homocysteine levels cause endothelial dysfunction, which alters the normal homeostatic response of the endothelium, causing increased thrombogenicity and hence increased platelet aggregation and enhanced oxidative damage of LDL.[8]

Many studies have found that elevated homocysteine levels are a risk factor for developing CAD.[9] However, factors responsible for hyper-homocysteinemia have genetic predisposition and also depend on the nutritional and lifestyle pattern of the population.[10]

Thus, the present study was aimed to evaluate the association between plasma homocysteine level and coronary artery disease in Indian patients.

2. Material & Methods

This case control study was conducted between January 2019 to January 2020 in a tertiary care hospital in North India. 237 diagnosed patients of ACS, admitted to the OPD/Emergency of the Cardiology department formed the study group and were compared with 50 age and gender matched apparently healthy controls.

All those patients were included in the study who were more than 18 years of age and presented with ACS (ST segment elevation myocardial infarction, Non-ST segment elevation myocardial infarction, unstable angina with ≥10 minutes of angina or angina equivalent consistent with unstable angina or myocardial infarction (MI) within 72 hours, with either elevated cardiac biomarkers (CK-MB or troponin) or ST segment deviation of >1mm ≥2 contiguous electrocardiographic leads). The patients with any of the following were excluded from the study: acute/chronic renal failure, chronic obstructive lung disease, any malignancy, liver failure, previous history of heart failure, moderate or severe valvular heart disease, peripheral arterial disease, aortic dissection, pulmonary embolism, cardiogenic shock, on treatment with statins or vitamin supplementation.

The study was approved by Institutional Research and Ethics Committee and written informed consent was taken from all participants at the time of enrolment.

A detailed history was taken from all the participants on a structured proforma. Venous sample was taken under all aseptic precautions and analysed for plasma levels of homocysteine apart from the routine investigations. Plasma homocysteine was estimated using chemiluminescence immunoassay on ADVIA Centaur XP system.

Statistical analysis was done using SPSS v.22.0. Values were expressed as a mean ± standard deviation or as percentages. The chi-square test was used to compare categorical variables, and the Student's t-test and Mann-Whitney U tests were used to compare parametric and non-parametric variables. Statistical correlations were assessed using Pearson's correlation analyses A p value < 0.05 was considered statistically significant.

3. Results

Clinical and laboratory characteristics of the subjects of the study are shown in Table 1. The conventional risk factors of CAD that were assessed included BMI, hypertension, diabetes, smoking and family history of CAD and lipid profile. Mean BMI was found to be significantly higher (26.9±2.8 kg/$m^{2)}$ in patients of CAD as compared to healthy controls (24.7±2.9). Smoking, hypertension, diabetes and family history of CAD was found to be significantly more prevalent in patients of CAD. The levels of total cholesterol, triglyceride, and LDL cholesterol were found to be significantly higher in patients of CAD ($p < 0.001$) as compared with control group while levels of HDL were lower in these patients.

The plasma homocysteine levels in the subjects of the study group are shown in Figure 1. The mean homocysteine levels were found to be significantly higher ($p<0.001$) in patients of CAD as compared to the healthy controls. (14.34 ± 7.49 µmol/L and 11.34 ± 4.91 µmol/L respectively).

The subjects of the study group were divided into four groups based on the presence of risk factor ie hypertension, diabetes, smoking, family of CAD (Table 2). However, no significant difference in the levels of homocysteine was found between patients of CAD with different conventional risk factors. There was also no significant correlation found between plasma homocysteine levels and parameters of lipid profile in the subjects of the study group.

Table 1: Clinical and laboratory characteristics of subjects of the study.

Parameters	Patients of CAD	Healthy Controls	P value
Age (years)	50.4±13.3	48.36±15.8	0.32
Male (n%)	76	80	0.53
Female (n%)	24	20	
Smoking (n%)	33.8	0	0.00
Hypertension (n%)	43.5	0	0.00
Diabetes (n%)	29.5	0	0.00
Family history of CAD (n%)	16.5	0	0.00
BMI (kg/m^2)	26.9±2.8	24.7±2.9	0.01
Total cholesterol (mg/dl)	185±52.1	158.34±43.8	0.001
Triglycerides (mg/dl)	167±75.6	119.5±63.0	0.00
HDL (mg/dl)	40.6±14.3	41.9±22.6	0.49
LDL (mg/dl)	110.4±45.5	78.1±37.2	0.00
VLDL (mg/dl)	33.88±15.9	24.8±12.8	0.00
Homocysteine (µmol/l	14.3±7.4	11.34±4.9	0.007

Table 2: Levels of homocysteine in patients of CAD categorized on the basis of conventional risk factors of CAD.

Conventional Risk factor	Number of subjects	Mean levels of homocysteine (µmol/l)
Hypertension	101	16.22 ± 8.46
Diabetes	69	16.05±8.8
Smoking	80	14.35±7.7
Family history of CAD	39	14.66±6.1

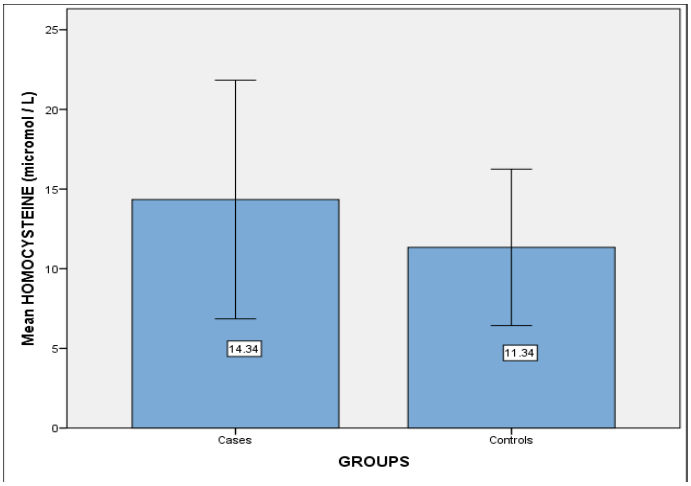

Figure 1: Levels of Homocysteine (µmol/l) in subjects of the study group.

4. Discussion

ACS is a term used to describe a range of myocardial ischemic states or CAD that includes unstable angina, NSTEMI, or STEMI. It is associated with major morbidity and mortality and causes a large financial burden on the health care system. The pathophysiology in CAD is decreased blood flow to the part of heart muscle which is usually secondary to thrombus formation and plaque rupture.

The conventional risk factors for CAD include dyslipidemia, HTN, DM, smoking, obesity and family history of CAD. Accurate diagnosis and early risk factor analysis is essential in guiding treatment and predicting the prognosis of patients with CAD. Inspite of the knowledge of these risk factors and measures to control them, there has been an increase in the incidence of the disease. Thus there felt a need to evaluate newer risk factors of CAD.

Plasma homocysteinehas been suggested to be an independent risk factor in pathophysiology of atherothrombotic vascular disease. Many studies have explored the role of levels of homocysteine as a risk factor for developing CAD. [6,11,12] In spite of multiple studies, the role of hyper-homocysteinemia as a risk factor of CAD is still disputed. Taking into consideration the genetic and ethnic variation in the levels of homocysteine, the present study was planned to evaluate the association between homocysteine and CAD in Indian patients.

The study subjects included 237 diagnosed patients with ACS, who were compared with 50 age and sex matched apparently healthy controls. The cases and controls were compared for the presence of conventional risk factors of CAD and newer risk factor i.e., homocysteine levels.

A male preponderance was seen in the subjects of the study group having CAD. The results are in line with similar results from earlier studies. [13-15] The mean BMI of the CAD patients was found to be higher as compared to the controls, in concordance with the results of another study that found higher BMI in CAD patients as compared to controls. [16]

Percentage of subjects with hypertension, diabetes, smoking and family history of CAD was significantly higher in cases as compared to the controls. Previous studies have also shown that high rates of CAD in Asian Indians are associated by high prevalence of these conventional risk factors. [17]

The mean levels of lipid profile were compared between the patients and healthy controls. CAD patients had higher levels of total cholesterol, triglycerides, LDL and VLDL (185 ±52.1 mg/d l167 ± 75.6mg/dl, 110.4 ± 45.5mg/dl, 110.4±45.5 mg/dl, 33.88 ± 15.9) as compared to healthy controls (158.34 ±43.8 mg/dl,119.5 ± 63.0mg/dl, 78.1 ±37.2 mg/dl, 24.8 ± 12.8mg/dl). The results are in line with a study conducted on Pakistani population which revealed elevated total cholesterol, triglyceride, VLDL and LDL in CAD patients as compared to healthy controls.[18]

Plasma homocysteine levels were found to be significantly higher in patients with CAD as compared to the healthy controls. ($P<0.05$) Similar results have been forwarded by a study conducted by Saeed Sadeghian *et al* that showed serum levels of homocysteine were significantly higher in CAD patients when compared to participants without CAD (19.3 ± 1.7 µmol/L versus 13.9 ± 0.9 µmol/L, $P = 0.005$).[19] Another study from south India also showed similar results (18.59 ± 2.63 µmol/L versus 11.69 ± 2.80 µmol/L, in cases and controls respectively, $P<0.001$).[20] Higher homocysteine levels in CAD have also been found by many other researchers on studies conducted in varied populations.[21-24]

In this study, no significant correlation was found between plasma homocysteine levels and other conventional risk factors of CAD i.e. hypertension, diabetes, smoking, dyslipidemia, obesity and family history of CAD. These results are similar to those reported by two earlier studies from India. [9,25]

The results of this study thus show that increased homocysteine is significantly associated with CAD and thus may be considered as a newer risk factor for CAD in Indian patients.

5. Conclusion

Homocysteine is one of the newer risk factors identified for CAD globally in the recent years. The results of this study suggest that homocysteine levels are associated with CAD and its measurement may routinely be done to assess the coronary artery disease risk assessment.

Limitations of the study

Being a hospital-based study results may not be generalizable. The sample size may have affected the results. Further study with larger sample size is warranted for more accuracy.

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