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Cardiology

Evaluation of an Independent Association between Homocysteine Levels and Coronary Artery Disease in Patients Undergoing Coronary Angiogram

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Abstract: Majority of patients who experience a Coronary Artery disease event have one or more of the conventional risk factors for atherosclerosis and so do many people who have not yet experienced such an event. Thus models based on conventional risk factors have a lesser accuracy to be attributed as a sole risk factor, providing a stimulus to search for new factors to predict accurately the risk of CAD. In this regard newer risk factors like homocysteine, Lp(a), insulin resistances are the important ones . This particular study was done with reference to homocysteine levels and its quantitative detection in patients with a clinical diagnosis of CAD, who were willing to undergo a coronary angiogram with the aim of finding an independent association between homocysteine levels and coronary artery disease in these patients. The study was planned such that these patients were divided into 2 groups, one with angiographic evidence of CAD and the other without angiographic evidence, the baseline patient characteristics were similar in both the groups, plasma homocysteine levels were assessed in both groups and the conclusion was a statistically significant higher value of plasma homocysteine in the group with angiographic evidence of CAD compared to the one without angiographic evidence of CAD thus establishing the role of homocysteine as an important and independent contributor to the development of CAD.

Keywords: Coronary artery disease (CAD), homocysteine, atherosclerosis.

INTRODUCTION

Coronary artery disease remains the major cause of morbidity and mortality in both developed and developing countries.

Smoking cessation and reductions in cholesterol levels and blood pressure have all been shown to be effective strategies in the prevention of cardiovascular disease [1]. However, these major, classic cardiovascular risk factors and non-modifiable risk factors such as age, sex, and family history cannot fully explain why some persons develop myocardial infarction, stroke, and other cardiovascular disease but other persons do not[2-4]. Therefore, there are other factors which contribute to thermogenesis and increase the likelihood of developing coronary artery disease. Among the many risk factors that have emerged, elevated plasma or serum levels of homocysteine is of particular interest. Epidemiological studies have shown that moderately elevated plasma homocysteine levels are highly prevalent in the general population and are associated with the increased risk for fatal or non-fatal cardiovascular disease, independent of the classic risk factors. This association is usually consistent, strong, dose-related and biologically plausible. Homocysteine is a sulfur-containing amino acid produced during the catabolism of the essential amino acid methionine. Homocysteine can be metabolized via two major pathways. In most tissues, homocysteine is re-methylated in a process that requires methionine synthase, vitamin B12 as a cofactor, and methyl tetrahydrofolate as a substrate. This pathway requires an adequate supply of folic acid and the enzyme methylene tetrahydrofolate reductase (MTHFR)[5]. Genetic and acquired abnormalities in the function of these enzymes or deficiencies in folic acid, vitamin B6, or vitamin B12 cofactors can lead to elevated homocysteine levels. Hyperhomocysteinemia is defined as a medical condition characterized by an abnormally high level (above 15 μmol/L) of homocysteine in the blood [6]. Total concentration of homocysteine in plasma of healthy humans (fasting) is low and its level is between 5.0 and 15.0 μmol/L when assessed with the use of HPLC, or 5.0-12.0 μmol/l when immunoassay methods are used [7]. Elevated plasma homocysteine may be an

important cause for atherosclerosis formation [8]. The adverse effects of homocysteine, involve oxidative damage to vascular endothelial cells, increased proliferation of smooth muscle cells, and oxidative modification of low density lipoprotein, all leading to atherosclerosis [9]. That elevated plasma homocysteine is an independent factor for CAD in Asian Indians as compared to Europeans was reported by chamber's *et al*. [10], also an indian study reported that methylenetetra hydrofolate reductase (MTHFR) gene mutation causing hyperhomocysteinemia as a risk for increased risk of CAD in Indians [11]. However, the result on hyperhomocysteinemia in CAD has been conflicting as several other studies have failed to demonstrate an association between homocysteine and CAD in Indians [12]. Thus the evidence for plasma homocysteine, as an independent risk factor in the community was not well understood. Of particular interest are nutritional deficiencies in the vitamin co-factors that are required for homocysteine metabolism: folic acid, vitamin B6, and vitamin B12. These deficiencies are highly prevalent and may account for most cases of hyperhomocysteinemia. An inverse relationship has been shown between plasma homocysteine levels and plasma levels and dietary intake of folate and vitamin B6 and vitamin B12 [13]. Many other cross-sectional and observational studies have examined the association between plasma homocysteine levels and cardiovascular risk, and most support the existence of such an association. Despite the enormous heterogeneity of studies, a 1995 meta-analysis of 27 observational studies involving a total of approximately 4000 participants reported that hyperhomocysteinemia was associated with an increased risk for fatal and non-fatal atherosclerotic vascular disease in the coronary and peripheral circulation[14]. Prospective longitudinal studies provide more robust evidence, especially when a strong and confident association between a risk factor and disease is found. Eight cohort studies reported statistically significant positive associations between elevated homocysteine levels and cardiovascular disease. Therefore, although there is enough evidence for an association between serum homocysteine and CAD, but there is scarcity of data addressing the importance of homocysteine as a risk factor for angiographic CAD in indian patients, and hence the present study was undertaken to evaluate the independent association between levels of homocysteine in patients of CAD undergoing coronary angiogram.

METHODS AND MATERIALS

The patients between the age of 30 and 70 years with a clinical diagnosis of CAD based on symptoms and/or stress test and those who were willing to undergo a coronary angiogram after an informed consent were selected for the study in the department of cardiology at Gandhi Medical College, Bhopal and LBS heart hospital, Bhopal from April 2013- March 2014. The study was approved from the ethics committee of the Institute and informed consent were obtained from patients. Patients with renal failure, hypothyroid patients and patients on antiepileptic drugs, niacin etc were excluded from the study. A total of 302 patients were henceforth included in the study, who were divided into 2 groups based on presence (group1,n=254) or absence(group 2,n=48) of angiographic evidence of CAD(evidence defined as ≥50% stenosis of one or more coronary arteries. Plasma homocysteine levels were assessed by HPLC method and a complete medical history, physical exam, ECG and routine lab investigations were done for all patients.

STATISTICAL ANALYSIS

The results were expressed as mean + SD unless stated otherwise, a probability value of $p<0.05$ was taken as statistically significant and coefficient of correlation was also assessed.

RESULTS AND DISCUSSION

The two patient groups had similar baseline characteristics at entry, variables like age, sex, weight, smoking, blood pressure and heart rates were compared between the two groups and p value was found to be statistically insignificant (Table 1).

The homocysteine level in group 1 was 28.6±13.8µmol/l and in group 2 was 13.2±7.24µmol/l which was found to be statistically significant (table 2).

Table-1: Comparison of parameters

Variables	Group 1(n=254)	Group 2(n=48)	P value
Age(years)	46±11.32	44±9.2	NS
Sex(no. of males)	200(78.7%)	40(83.3%)	NS
Weight(kg)	64±12	70±12.7	NS
Smokers	112(44%)	19(40%)	NS
SBP(mmhg)	142±16.9	144±17.4	NS
DBP(mmhg)	97±6.9	96.2±7.7	NS
Heart Rate(beats/min)	82±6.9	81±5.9	NS

Table-2: Homocysteine levels

Variable	Group 1(n=254)	Group 2(n=48)	P value
Homocysteine level(µmol/l)	28.6±13.8	13.2±7.24	0.05

The Pathologic and epidemiological studies suggest that only about one half to two thirds of the variation in anatomic extent of atherosclerosis and risk for atherosclerotic vascular disease can be explained by classic risk factors, as a result many emerging risk factors have been investigated, among these elevated plasma homocysteine levels are of importance, in the present study 302 patients who were undergoing CAG were taken up and homocysteine levels in them were analyzed, our observations together with those of other meta-analysis showed a statistically significant increase in total homocysteine levels with angiographic proven CAD(group 1). In our study risk factors both modifiable and non-modifiable like age, sex, weight, smoking, blood pressure, heart rates were compared between the two groups

CONCLUSION

In conclusion, our data suggests that plasma homocysteine levels were increased significantly in CAD patients when compared to controls and that hyperhomocysteinemia is a significant and independent risk factor for angiographic coronary disease irrespective of baseline lipid profile of the patients and patients with hyperhomocystinemia present more often with unstable coronary syndrome and angiographically more severe CAD. Henceforth, selective screening should be considered in those with a) strong family history and b) suspected elevated levels of homocysteine.

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