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ASSESSMENT OF THE LEVEL OF HOMOCYSTEINE AND ITS CORRELATION WITH THE DEGREE OF SEVERITY OF CAD BY CORONARY ANGIOGRAPHY

Ajay Sharma Associate Professor, Department of Cardiology, Gandhi Medical College, Bhopal, India

Abhinav Nair* Resident, Department Of Medicine, Gandhi Medical College, Bhopal, India *Corresponding Author

Rohit Shrivastava Consultant Cardiologist, LBS Heart Hospital, Bhopal.

Bhoopendra Bhadauriya Resident, Department Of Medicine, Gandhi Medical College, Bhopal, India

ABSTRACT

Cardiovascular diseases which comprise of diseases of the heart and the blood vessels, are believed to account for about 1/3rd of all the deaths worldwide with the prevalence still on a steep rise. There are multiple contributory factors to this disease, thus making it difficult to pin-point a single factor responsible. Homocysteine has been recognized as a risk factor as early as 1990s, for the presence of atherosclerotic vascular disease and hypercoagulability states. There has been a long standing debate regarding to the extent to which homocysteine should be considered as a risk factor for CAD, and as such many authors doubt this association. Hence this study was planned to assess the levels of homocysteine in patients presenting with a clinical diagnosis of CAD and then correlating it with the degree of severity of CAD by coronary angiography. The summary was a statistically significant higher levels of mean plasma homocysteine in patients with TVD compared to DVD and SVD, thus establishing that severity of angiographically detected CAD is positively associated with the persons total homocysteine levels.

Introduction:

Cardiovascular deaths which account for about 35 % of the worldwide mortality is among the diseases which have a multitude of risk factors and the prevalence of which is on the rise(1). Using the Gensini scoring system , the severity of coronary artery disease is classified as single vessel, double vessel or triple vessel disease(2). Since the early 1990's, homocysteine has been recognized as a risk factor for atherogenesis, a pathological mechanism widely responsible for CAD, stroke and other cardiovascular disease states (2). Some researchers believe that only 50% of cardiovascular deaths can be explained by "classical" risk factors and believe that "novel" risk factors could be responsible for more than what was previously thought as a contributor to cardiovascular disease states(3). For the purpose of use as a screening tool, a risk factor should be strongly and causally associated with the target disease, and many authors doubt whether such a relationship between homocysteine and CAD exists(3). Research has indicated towards a relationship between moderately elevated homocysteine levels and the risk of CVD (coronary, heart, cerebrovascular and peripheral artery diseases)(3). The homozygous mutation of C,S can cause severe hyperhomocysteinemia where homocysteine concentration is up to 40-fold of the normal levels. This disease occurs in approximately 1 of 100,000 live births(3). When untreated, a vascular event (stroke, myocardial infarction, other thromboembolic complication) occurs in about half of these patients before the age of 30. Another cause of rare, genetically mediated severe hyperhomocysteinemia is due to homozygous mutations of MTHFR. People with these mutations have been noted to have premature cardiovascular diseases(3). But a large meta-analysis showed the lack of statistically significant association between MTHFR mutations and coronary heart disease except in Middle East and Japan, where it portrayed statistical significance. In a study done on rats, homocysteine was found to be an independent risk factor for atherosclerosis and hence CAD. McCully in 1969 was one of the first to propose a causal relationship of hyperhomocysteinemia with development of atherosclerotic disease and it is well established that atherosclerosis is the most common pathological process that leads to cardiovascular diseases such as MI(myocardial infarction), stroke and heart failure(1). Several cross-sectional and case control studies have pointed towards a clear correlation between total serum homocysteine and the incidence of coronary, carotid, and peripheral vascular disease (5). Homocysteine through its many mechanisms affecting the vascular endothelium and smooth muscle cells such as endothelial dysfunction, oxidative damage, an increase is synthesis of collagen and deterioration of arterial wall elastic material can lead to the development of CAD(6). It also leads to arteriosclerosis, which is a process of continued inflammatory damage to the arterial intima leading to plaque formation, fibrosis and calcifications(7). That homocysteine is an early predictor of atherosclerosis was observed in a study using 70 participants (70 patients undergoing coronary angiography at Kasturba Hospital, Manipal University) Shenoy et al(2). Homocysteine levels were higher in patients with CAD compared to those without CAD and also there was a significant association of homocysteine levels with the severity of CAD. The most probable mechanism ascertained was endothelial dysfunction promoting cardiovascular disease.(2) An increased cholesterol level promotes atherosclerosis and hence it is a risk factor for CAD. Serum levels of homocysteine were found to be significantly higher in CAD than in non CAD subjects. Increased serum homocysteine levels positively correlated with severity of CAD(2). The role of homocysteine in endothelial dysfunction is thought to be mediated by mechanisms including oxidative stress, nuclear factor-kb (NF-kb) activation, inflammation, and inhibition of endothelial nitric oxide synthase (eNOS)(8). Upon adding the genetic and nutrition related factors, we may be having another contributing factor which is that Epigenetic directive of cardiovascular development and cardiovascular stem cell biology may be related to predilection to cardiovascular disease and CAD(9). Nutritional deficiencies and environmental exposures in utero or any such critically ill periods of life, can lead to epigenetic alterations in the expression of genes, contributing to disease risk of atherosclerosis, hypertension, CAD in later life(9). A dietary deficiency of vitamin B12, folate or choline may lead to such outcomes as these are factors necessary for methylation reactions(9). The association of homocysteine with blood pressure is an area of attention because blood pressure may mediate part of the cardio-toxic effect of homocysteine, A causal link exists between homocysteine and blood pressure and it is reinforced by experimental and animal studies that have reported a rise in blood pressure as a consequence of induced hyperhomocysteinemia(10), due to its effect on vascular integrity, homocysteine may be responsible for elevation of blood pressure through numerous mechanisms and thus leading to CAD(10). Along with the effects of hyperhomocysteinemia mentioned before, this study indicates that it adversely affects the biosynthesis and function of vasodilator factors in the vascular wall, in turn contributing to endothelial cell division restriction, myocyte proliferation and impaired production of extracellular matrix components(11). Hyperhomocysteinemia may lead to biochemical effects on

endothelium and cause damage to endothelial cells, diastolic dysfunction of vessels and reduction of flexibility due to its influence on vascular wall remodeling(11), these factors can most definitely affect the coronary arteries as well and lead to CAD and myocardial infarctions. A substantial body of evidence is present to suggest an association between cardiovascular risk and plasma homocysteine levels. Although this association has seemed to be quite consistent, not all studies have demonstrated that reducing the levels of homocysteine will result in a reduced risk of cardiovascular disease. There is scarcity of data addressing the importance of levels of homocysteine as a risk factor for angiographic CAD in indian patients and hence this study was planned to delineate this correlation.

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, blood sample was drawn after 6 hours of fasting, and a complete medical history, physical exam, ECG and routine lab investigations were done for all patients. The patients who were in group 1(n=254), were classified as having single vessel disease(SVD), double vessel disease(DVD) and TVD (triple vessel disease) and levels of plasma homocysteine were compared among them.

Results and discussion:

The patients in group 1 with angiographic evidence of CAD (n=254), were divided into 3 groups based on whether they had single vessel disease(SVD), double vessel disease(DVD) and triple vessel disease (TVD).(table 1) . In group 1, single vessel disease was seen in 84 patients(33%), double vessel disease was seen in 92 patients (36%) and triple vessel disease was seen in 78 patients (31%).

Table 1

SVD(No. of patients)	DVD(No. of patients)	TVD(No. of patients)	Total patients in group 1
84(33%)	92(36%)	78(31%)	54

The mean plasma homocysteine levels were compared in the patients of group 1- mean plasma homocysteine level in patients with single vessel disease was 19.3±10.1µmol/l, in double vessel disease it was 23.16±11.32µmol/l and in triple vessel disease it was 30.1±17.3µmol/l. (table 2)

Table 2

Variable	SVD	DVD	TVD
Homocysteine level (µmol/l)	19.3±10.1	23.16±11.32	30.1±17.3

The present study clearly indicates a statistical significance in the correlation of mean levels of plasma homocysteine with angiographic severity of CAD by coronary angiogram, as it is seen that highest mean plasma levels of homocysteine was seen in patients with triple vessel disease (TVD) followed by double vessel disease(DVD) and single vessel disease(SVD). Our observation together with those of other meta-analysis showed a statistically significant increment in total homocysteine levels with angiographic proven CAD, we also found that severity of angiographically detected CAD is positively associated with the person's total homocysteine level, similar findings were reported by Wald et al, in thrombosis research in 2003.

Conclusion:

According to our study, we conclude that hyperhomocysteinemia is a significant and independent risk factor for angiographic coronary artery disease and levels of homocysteine correlate linearly with the severity of CAD on coronary angiography, thus it is only imperative that selective screening be considered in those with a strong family history and in those suspected of having elevated levels of homocysteine.

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