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HOMOCYSTEINE AND ACUTE MYOCARDIAL INFARCTION

Saatea Arif [1], Ghosia Lutfullah[2], Bushra Iftikhar[1], Jamil-ur-Rahman[1], Muhammad Rashid Waheed[3], Sunia Arif Khan[1]

[1]Khyber Medical College, Peshawar - Pakistan

[2]Centre of Biotechnology, University of Peshawar - Pakistan

[3]Ayub Medical College, Abbottabad - Pakistan

ABSTRACT

Objective: To evaluate the presence of hyperhomocysteinemia in patients of acute myocardial infarction(AMI) and to analyze the relationship between total homocysteine and physical activity and serum cholesterol levels.

Material and Methods: A cross sectional study was conducted which included 200 patients of acute myocardial infarction studied in two age groups of 25-45 years and 46-70 years, and an equal number of age and sex matched controls. Serum total homocysteine was analyzed by Fluorescence Polarization Immunoassay method on Abbott IMX, (Immunoassay analyzer) and determination of serum cholesterol was done by kit method (Elitech diagnostics, Spain).

Results: Moderate hyperhomocysteinemia was recorded in younger patients of AMI (23.76 ± 2.08 μmol/L and 20.21 ± 4.17 μmol/L respectively in male and female patients). Older patients of AMI showed intermediate hyperhomocysteinemia in male patients as compared to female patients (44.62 ± 2.04 μmol/L and 29.84 ± 1.86 μmol/L respectively in male and female patients). Moderate hyperhomocysteinemia was noted with increasing age in the control subjects of our general population. There was no patient with normal homocysteine level. Only three patients had no risk factor under study, two patients presented with both risk factors i.e. physical inactivity and raised cholesterol levels, and the rest of the patients had either of the two risk factors. Serum homocysteine showed a strong relationship with cardiovascular risk factors as markedly elevated total homocysteine was recorded in the patients of acute myocardial infarction who were exposed to either one or both of these risk factors as compared to controls.

Conclusion: Hyperhomocysteinemia is a risk factor for coronary artery disease in our population, perhaps through an interplay with physical inactivity and raised serum cholesterol levels.

Key words: Hyperhomocysteinemia, cardiovascular risk factors, acute myocardial infarction.

INTRODUCTION

Naturally occurring sulphur containing amino acid homocysteine is derived as an intermediate compound during the metabolism of methionine. Serum / plasma level of homocysteine is dependent on genetically regulated levels of essential enzymes taking part in its metabolism, which depends on the intake of folic acid,vitamin B_6 and vitamin B_{12}.[1] Moderate elevation of homocysteine is a risk factor for atherosclerotic disease in the coronary, cerebral as well as peripheral arterial vessels[2]. Normal concentration of total homocysteine in the serum/plasma is taken upto 15 μmol/L. Moderate and intermediate hyperhomocysteinemia refers to homocysteine concentration in the range of 16-30 μmol/L and 31-100 μmol/L respectively.[3] Total homocysteine is derived from methionine metabolism and it can be degraded through two enzymatic pathways: The remethylation pathway in which total homocysteine receives a methyl group from the folate cycle to be reconverted to methionine. The methionine so formed is activated by adenosine triphosphate to form| 5-adenosyl methionine which serves as a methyl donor. In the trans sulfuration pathway total homocysteine is condensed with serine to form cystathionine by cystathionine beta synthase which needs the active form of vitamin B_{12} as cofactor. Subsequently cystathionine is converted to cysteine through another vitamin B_6 dependent reaction.[4]

Moderate hyperhomocysteinemia is an established risk factor for arterial and venous thrombosis. The thrombogenicity of homocysteine resides in its ability to modify the endothelial resistance to thrombosis by several mechanisms. Among these are the induction of oxidative stress which enhances the tissue factor expression on endothelial cells, the increase of platelet thromboxane production and the promotion of anti fibrinolytic effect of lipoprotein (a) levels. In addition short term exposure of smooth

Address for Correspondence:
Dr. Saatea Arif
Associate Professor
Department of Biochemistry
Khyber Medical College, Peshawar
Contact No. 091-9216206 Ext. 164
Email: saateaarif@yahoo.com

muscle cells to homocysteine increases DNA synthesis, induces cyclin A gene expression and favors the release of mitogenic factors leading to cell proliferation and migration.[5] In recent years several epidemiological observations that have linked hyperhomocysteinemia to increased risk of cardiovascular problems are of the view that homocysteine is an independent risk factor for coronary artery diseases.[6-9] However an association between homocysteine levels and cardiovascular risk factors has been demonstrated by many research workers[10-14].

The objective of this study was to find out the frequency of hyperhomocysteinemia in the patients of acute myocardial infarction and to see the level of serum homocysteine in the presence and absence of physical activity and serum cholesterol levels.

MATERIAL AND METHODS

This study was carried out in Pakistan Medical Research Council KMC Peshawar in collaboration with cardiology departments of Post Graduate Medical Institute Lady Reading Hospital and Khyber Teaching Hospital Peshawar and Abbott Laboratories Research Division Pakistan. The study population included 100 patients of acute myocardial infarction in two age groups of 25-45 years (with 58 males and 42 females) and 46-70 years (in which 52 patients were males and 48 were females). Another 100 gender matched control subjects were also included in the study.

Table 1: Subjects characteristics and Serum Homocysteine levels

Group/ Subjects	Sex	Age (Mean ± SD)	Serum Homo-cysteine (mean ± SD) (μ mol/L)
A (25-45 years) Patients (n = 100)	Male n=58	38.45± 2.36[b]	23.76 ± 2.08[c]
	Female n=42	41.60 ± 1.90[a]	20.21 ± 4.17[c]
B (25-45 years) Controls (n = 100)	Male n=58	42.72 ± 2.90	12.92 ± 5.04
	Female n=42	42.30 ± 5.63	10.44 ± 2.28
C (46-70 years) Patients (n = 100)	Male n= 52	57.19 ± 1.80[b]	44.62 ± 2.04[c]
	Female n = 48	58.40 ± 2.70[C]	29.84 ± 1.86[c]
D (46-70 years) Controls (n = 100)	Male n= 52	56.80 ± 2.71	18.89 ± 2.62
	Female n = 48	63.10 ± 1.21	16.62 ± 2.78

a = Non significant, b = Markedly significant (P < 0.01), c = Highly significant (P < 0.001)

Exclusion criteria from the study for patients and controls were subjects in renal failure, having thyroid disorders, psoriasis, malignancy and megaloblastic anemia. Control subjects had no recent or previous history of coronary artery disease, angina, congenital heart problem, hypertension or hypercholesterolemia.

Physically active patients in the present study were the ones who had given the history of daily cycling , gardening, walking for more than half an hour in the morning and after noon for going to jobs, strenuous physical work on daily wages and 6% patients who performed brisk walk for a minimum of half hour daily.

Informed consent was taken from each patient and control. Data was collected through questionnaire, examination and blood tests.

Sample collection and Biochemical analysis: A fasting blood sample was collected immediately after examination and transported to laboratory on ice. Serum was separated within one hour of sample collection by ultracentrifugation at 1000 x g for 10 minutes. Serum cholesterol was estimated immediately by Elitech kit and rest of the serum was stored frozen at "-20°C". Serum homocysteine was analyzed in batches by Fluorescence Polarization Immunoassay principle on automated immunoassay analyzer (Abbott IMX).

Statistical Methods: Data analysis was done on SPSS 10 soft ware. The numerical and categorical data was presented as means. Means of serum total homocysteine and serum cholesterol of patients and controls were compared using 'z' test and p value was calculated for appropriate degree of freedom.

RESULTS

The characteristics of the study population are shown in Table 1. Mean age of female patients of acute myocardial infarction and controls was higher in both age groups , but serum total homocysteine was higher in men than in women and increased progressively with age in both sexes. The data shows that younger age group patients (both male and female) had moderate hyperhomocysteinemia but patients of age above forty five years showed intermediate hyperhomocysteinemia where homocysteine levels of male patients were highly raised (44.62 ± 2.04 μmol/L). The female patients of the same age group showed border line intermediate hyperhomocysteienmia (Mean serum total homocysteine, 29.84 ± 1.86 μmol/L). This age related increase in serum homocysteine was also seen in control subjects aged above forty five years. Figure 1 shows highly raised mean homocysteine levels of male and female patients who performed less physical activity. Physically active patients showed moderate hyperhomocysteinemia (19.5 μmol/L and 18.41 μmol/L respectively in male and female patients).

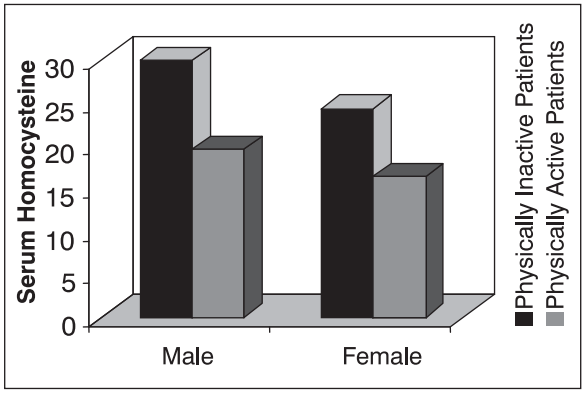

Fig. 1: Serum Homocysteine levels

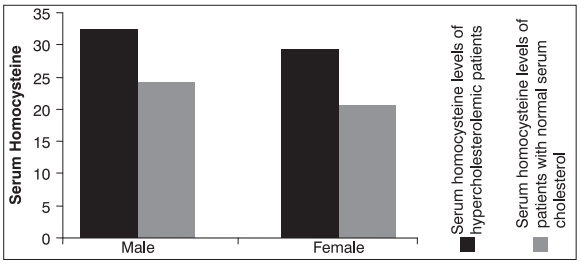

Fig. 2: Serum Homocysteine vs Cholesterol levels

Similarly there was a significant difference in the mean homocysteine concentrations of hypercholesterolemic patients and the ones with normal serum cholesterol. (Figure 2). The results of this study how ever show that the difference in homocysteine levels of physically inactive and active patients was more significant than the difference in homocysteiene concentrations in the patients with raised and normal cholesterol . This puts an emphasis on the beneficial effects of exercise on the prevention of cardiovascular risk factors.

DISCUSSION

Our study findings support the hypothesis that hyperhomocysteinemia is associated with coronary atherosclerosis and aging but not independent of traditional risk factors. The results of present study reveal a higher prevalence of hyperhomocysteinemia in the patients compared to controls in both age groups but the control subjects of age above forty five years also showed moderate hyperhomocysteinemia and the incidence was more in male controls than in the females. There are a variety of reasons why elderly people are more at risk of hyperhomocysteinemia than the young ones. One of the important cause is higher prevalence of drug intake and low vitamin bioavailability due to atrophic gastritis or gastric hypoacidity in old age. Inadequate B vitamin status is associated with reduced immune and cognitive function[17]. Available data indicate that in addition to elderly high risk patients , hyperhomocysteinemia is a risk factor of cardiovascular events in patients with coronary artery disease[18]. Numerous in vitro and in vivo studies[19,20] have shown that elevation of homocysteine induces endothelial dysfunction or damage. It exerts its damaging effects on endothelium through mechanisms involving reactive oxygen species. Homocysteine contains a free sulfydryl group that when oxidized to disulfide produces super oxide anions and hydrogen peroxide. The oxidative stress thus produced damages the endothelium and causes inflammation which plays an essential role in all stages of atherosclerosis process[21].

The results of present study suggest that the risk of sudden acute myocardial infarction is increased in hyperhomocysteinemic patients exposed to traditional risk factors.

Physically inactive patients in the present study have shown intermediate hyperhomocysteinemia especially with advancing age. Some studies[22,23] have shown that physical inactivity increases body lipids and subsequently the deposition of atheromatous plaques in blood vessels which causes injury to the vessel walls. A slight increase in homocysteine concentration (especially in people with clinical and sub clinical deficiency of vitamin B_6, B_{12} and folic acid) are an additional risk to the subjects as homocysteine gets deposited on already existing plaques. Since vitamin B_{12} deficiency is more common in older age, it is likely that physically inactive older people have higher homocysteine concentration. There is a reduction in the risk of coronary artery disease by mild to moderate physical activity and a general benefit has been demonstrated in older age group[24]. Since this effect of exercise can not be fully explained by changes in other established risk factors, decreased serum total homocysteine concentration may contribute to the beneficial effect of physical activity on coronary risk.

Incidence of moderate hyperhomocysteinemia in all hypercholesterolemic patients in the present study is in accordance with the work done previously[25] Several mechanisms may be involved in the association between hyperhomocysteinemia and raised serum cholesterol. Homocysteine may directly damage the vascular matrix by affecting the biochemical and biosynthetic functions of vascular cells . Homocysteine thiolactone, a highly reactive anhydrous product of homocysteine oxidation combines with low density lipoprotein (LDL) to form aggregates that are taken up by intimal macrophages and incorporated into foam cells within the nascent atheromatous plaques. A multiplicative increase in the risk of vascular diseases in the presence of hyperhomocysteinemia may be related to the effect of homocysteine on lipid peroxidation and the vascular toxicity of oxidized LDL has been linked to its content of lipid peroxidation products[26]. Recently Connie and

colleagues [27] have reported that homocysteine may stimulate cholesterol biosynthesis in Hep-2 cells in humans. They investigated the underlying mechanisms for homocysteine induced hepatic cholesterol biosynthesis in an animal model by feeding a high methionine diet to rats for four weeks. The m RNA expression and the enzyme activity of 3 – hydroxyl -3 – methylglutaryl coenzyme A (HMG – Co A) reductase were significantly increased in the livers of these hypercholesterolemic rats. There was marked hepatic lipid accumulation , and an elevation of plasma cholesterol concentration. Three transcription factors namely Sterol regulatory element binding protein 2 (SREBP – 2), c AMP response element binding protein (CREB) and nuclear factor Y (NF – Y) were activated in their livers. Hyperhomocysteinemia and the formation of highly atherogenic oxycholesterols pose an additional risk to sudden acute and already existing cardiovascular problems and are now considered as one of the important cause of cerebrovascular accidents.

CONCLUSION

Homocysteine is an important risk factor for coronary artery disease. Its levels are affected by increasing age, male gender and life style factors. Comprehensive life style modification is, therefore, suggested to decrease the levels of circulating total homocysteine and the risk of coronary artery disease.

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