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Original Article

Association of Folic Acid Deficiency with Ischemic Heart Disease

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Abstract

Background: To assess the association between folic acid deficiency and ischemic heart disease

Methods: In this observational study patients of 25-65 years of age with newly diagnosed ischemic heart disease were included. All the patients on folic acid or vitamin B_{12} therapy, pregnant females, patients with any type of malignancy or patients with history of megaloblastic anemia were excluded from the study. A 3-5ml serum sample for the estimation of folic acid levels were obtained. Tests were performed using chemiluminescent Microparticle Immunoassay (CMIA). Odds ratio was determined to measure association between folic acid deficiency and ischemic heart disease.

Results: Folic acid level was assessed both in cases and controls, with a mean folic acid level of 4.19±2.11ng/mL among patients and in controls mean folic acid level was 5.05±1.67ng/mL (p-value=0.015). Folic acid deficiency was found in 41.7% in cases . Odds ratio was 2.347 (95% CI; 1.067, 5.162, p<0.05).

Conclusion: Folic acid deficiency was found high significantly in patients with ischemic heart disease as compared to that of controls and risk of ischemic heart disease is higher in patients with folic acid deficiency.

Key Words: Folic Acid Deficiency, Ischemic Heart Disease,

Introduction

It is recognized that folates have a beneficial role in the prevention of cardiovascular diseases. For the last few years, several studies have reported beneficial impact of folic acid on endothelial function, which is a surrogate end point for risk of cardiovascular diseases. In Pakistani population folic acid deficiency is highly prevalent . Folic acid is the parent compound of a family of folate compounds.[1] Humans cannot synthesize folic acid from various metabolites de novo and thus have to rely on dietary intake for sufficient levels of this vitamin. Citrus fruits, juices, dark green leafy vegetables such as spinach, wheat and other whole grains, and liver are the rich sources of Folic acid.[2] Different studies have shown that due to its biochemical functions folic acid can reduce Homocysteine levels within the blood and these levels can be used as biomarkers for detection of folate deficiency.[2,3] Clinical and epidemiological studies have shown a strong relationship between total plasma homocysteine levels and ischemic heart disease.[4,5]These are non communicable diseases having association with sedentary life style and dietary habits[6] and are considered a major health problem world wide.[7]

Folic acid also reduces atherosclerosis and improves endothelial dysfunction and prevents cardiovascular diseases.[8] Both of these are the major culprits in the pathogenesis of ischemic heart disease. Recently conducted Indian study shows strong association of folic acid deficiency with development of coronary artery disease.[9] In this study folic acid levels were significantly lower in patients of ischemic heart disease as compared to healthy controls .

In Pakistani population folic acid deficiency is highly prevalent, which appears to be a major cause of hyperhomocysteinemia.[10] Lower intake of fresh fruits and overcooking of food could be the cause of deficiencies of these micronutrients As it is concluded in one recent local study that folic acid deficiency below 5.5ng/ml leads to increase in levels of homocysteine. It could be assumed that folic acid deficiency is one of the causes for hyperhomocysteinemia in our population.[10]

Folic acid therapy on long term basis markedly improves the arterial endothelial functions not only in patients of unstable coronary artery disease with hyperhomocysteinemia but also in healthy cigarette smokers.[11] Therefore, there is a great need to look into the fact that if there exists any association between the patients of ischemic heart disease and folic acid deficiency. If this is really the fact, then clinicians should be advised that simple non toxic, relatively inexpensive folic acid supplementation may potentially reduce the risk of ischemic heart disease.

Patients and Methods

This case control study was conducted at HolyFfamilyHospital in department of pathology in

collaboration with cardiology department ,from February to August 2012. Patients of 25-65 years of age of either gender having ischemic heart disease (Newly diagnosed Patients presenting with sudden chest pain radiating to left arm and left side of neck with obvious ECG changes (ST Elevation ≥2mm in two consecutive chest leads or ≥1mm in two consecutive limb leads) or Non-ST Elevation MI (ST Depression, Q wave, T wave inversion) and elevated cardiac enzymes (TroponinT (positive) and or CKMB(≥25U/L) were included in the study as cases while all healthy individuals of matching age and sex attending Medical OPD were taken as controls. All the patients on folic acid or vitamin B_{12} therapy, pregnant females, patients with any type of malignancy or patients with H/O of megaloblastic anemia were excluded from the study.Patients were categorized in two groups as cases and controls. A 3-5ml Serum sample for the estimation of folic acid levels were obtained in gel bottle. All samples were processed in pathology laboratory of RMC and Allied Hospitals within 24 hours of collection. Tests were performed using chemiluminescent . Normal folic acid levels were 05-17ng/mL. Statistically data was analyzed by using SPSS version 21. For quantitative variables, like age, folic acid levels mean and SD was calculated. Independent sample t- test was used to compare folic acid levels in two groups. A p-value of $\leq$0.05 was considered to be significant statistically. Odds ratio was determined to measure association between folic acid deficiency and ischemic heart disease.

Results

Total 120 patients meeting inclusion criteria were enrolled in study; 60 in each group. The mean age of all cases was 53.85±8.99 and controls were 50.43±9.92 years . Among cases 88.3% were male and 11.7% were females while among controls there were 90% male and 10% females (Table 1). Majority of cases showed positive Trop T (Table 2). ST segment elevation was seen in 77%(Table 3).Mean folic acid levels in cases were 4.19±2.11 (ng/mL) and among controls mean folic acid level was 5.05±1.67.The difference was statistically significant (Table 4). Mean folic acid level was low in cases as compared to controls. i.e. (p-value=0.015). Among cases, 41.7% were found to be folic acid deficient and among controls, folic acid deficiency was found in 23.3%. The odds ratio was calculated as i.e. 2.347 (95% CI; 1.067, 5.162, p=0.032)

Table-1: Age distribution of patients and controls

	Cases	Controls
Age (years)		
	53.85±8.99	50.43±9.92
Sex		
Male	53(88.3%)	54(90%)
Female	7(11.7%)	6(10%)

Table 2. Ischemic heart disease -Trop T

Test Trop T	Percentage of patient
Positive	87%
Negative	13%

Table 3: ECG finding in Cases

ECG Finding	Percentage of Patient
STEMI	77%
NON STEMI	23%

Table 4. Folic acid level/deficiency in cases and controls

		Cases	Controls	Significance
Folic acid (ng/dl)		4.19±2.11	5.05±1.67	0.015
Folic Acid	Deficient	25(41.7%)	14(23.3%)	0.032
	Normal	35(58.3%)	46(76.7%)	

Odds ratio = 2.347 (95% CI; 1.067, 5.162)

Discussion

Hyperhomocysteinemia is generally known to be a cause of endothelial dysfunction, which further predisposes the endothelium to atheroma formation, which may lead to thrombo-embolism, causing coronary heart disease.[12,13] Plasma homocysteine levels were found to be high in South Asian population living in Great Britain in a recent study carried out in the UK. It was supposed that it might be a contributing factor to Coronary Heart Disease (CHD) related deaths in this group compared with European whites.[14,15]

Epidemiological transition has resulted in a new trend of morbidity and mortality due to vascular diseases. This has predominantly been seen in developing countries that account for 80% of the global burden of vascular disease[16]. In these countries patients of cardiovascular diseases, with normal biological markers, are not unheard of. This has led to a quest for newer causative factors, of which plasma homocysteine levels has emerged as a significant marker for vascular injury .[17-19] It has been studied by many scientists that homocysteine decreases in plasma with increase in folate levels.[10,13,20]

Seema Bhargava in her study assessed the role of

serum folic acid and vitaminB12 deficiencies as a major cause of high plasma homocysteine levels in patients of Northern region of India presenting with various pattern of vascular diseases. Folic acid levels were low (though well within the biological reference) in the patients of vascular diseases as compared to that of controls.[9] Statistically significant correlation of homocysteine levels with concentration of folic acid levels in controls as well as patients was found. In controls, homocysteine levels showed a significant negative correlation with folic acid levels. Also in patients, the negative correlation between homocysteine and folic acid levels was markedly significant. In patients of Coronary Artery Disease (CAD) and Cerebrovascular disease (CVD), negative correlation was significant, but in PVD patients, this negative correlation was insignificant.

According to the results reported by Guo et al plasma homocysteine levels in patients of unstable angina group was significantly (p-value<0.01) higher as compared to that of control group (10.7±5.3 vs. 19.2±4.9), while folic acid and Vitamin B12 levels were also significantly lower (p-value<0.05) (7.0±2.5 vs. 5.1±2.0). All conventional coronary artery risk factors like male sex, cigarette smoking, old age, diabetes mellitus, high cholesterol levels and high blood pressure were related to the elevated plasma homocystiene levels.[21,22]

Elevated levels of homocysteine in plasma are having association with cardiovascular disease, however the precise levels associated with high risk is yet controversial. A beneficial effect of folic acid interventional therapy on arterial endothelial function persists over longer periods is not known. Few studies suggest that patients having ≥3 risk factors of coronary artery disease, plasma homocysteine concentration was found high significantly and folic acid supplement therapy may be useful in lowering homocysteine levels and so arterial endothelial function can be improved.[23, 24] Folic acid therapy also improves endothelial function significantly in healthy cigarette smokers and during pregnancy. [25]Homocysteine initiates atherogenic effects by stimulating chemokine responses in endothelial cells involved in atherogenesis and folic acid therapy may down regulate these inflammatory responses. Supplementation of Folic acid to patients with hyperhomocysteinaemia has resulted in a low total plasma homocysteine levels. Moreover, a tendency to reverse the coagulation status and oxidative stress was noted.[26-29] Hyperhomocysteinemia is associated with a higher risk of ischemic injury to myocardium in patients presenting with acute coronary syndrome. Elevated plasma concentrations of homocysteine at time of admission also strongly predict cardiac events at later stage in patients of acute coronary syndromes.[30-32] It is also predicted that folic acid might have direct antioxidant role on the endothelium and folic acid could improve endothelial function directly. Prolonged folic acid supplementation therapy improves arterial endothelial function and has a potential role for the prevention of atherosclerosis in subjects with hyperhomocysteinaemia.[26 ,33] Moens et al. recently studied and concluded that folic acid also has direct substantial antioxidant effects, not only in the human vasculature but also inside myocardium. Indeed, it was stated that folic acid by scavenging reactive oxygen species which is responsible for its oxidation during experimental ischemia and reperfusion, prevents oxidation of BH4 in myocardium ,resulting in an improvement of eNOS dimerization and coupling. It is therefore assumed that decreased bioavailability of 5-MTHF may induce uncoupling of eNOS both in the vascular wall as well as myocardial tissue.[34, 35]

Conclusion

1.Folic acid deficiency was significantly high in patients with ischemic heart disease as compared to that of controls and risk of ischemic heart disease is higher in patients with folic acid deficiency.

2. Micronutrient supplementation, in known cardiac patients, needs consideration .

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