

## EFFECT OF FOLIC ACID ON SERUM HOMOCYSTEINE LEVELS IN PATIENTS WITH CARDIOVASCULAR DISEASES (CVD)

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Received: 21/08/2016

Revised: 27/11/2016

Accepted: 12/12/2016

### ABSTRACT

**Background:** Previous studies have demonstrated a reduction of serum homocysteine levels through the supplementation of folic acid. Aims - To evaluate the effect of folic acid (5mg) supplementation for five months on serum homocysteine levels in patients suffering from cardiovascular diseases. **Material & Methods-** The present prospective was conducted in the Department of Medicine of our tertiary care hospital from April 2015 to Jan 2016. The study recruited 50 patients who were admitted with the chief complaints of chest pain aged > 40 yrs of age as the test group. Study subjects in the test group were administered 5 mg folic acid per day orally for five months in addition to their drug regimen. Venous blood samples were collected after overnight fasting at baseline and after 5 months for the assessment of Serum total homocysteine, serum total glyceride, total cholesterol and high density lipoprotein. **Results-** The serum levels of homocysteine were significantly higher in the test group than control group at baseline ( $p < 0.005$ ). In the test group, Serum homocysteine levels, TC, TG, LDL, SBP, DBP observed a statistically significant reductions from baseline at 5 months after administration of folic acid ( $p < 0.005$ ). This reduction was observed in all the study subjects whether they were smokers/ non smokers, alcoholics/non alcoholics, suffered from angina or acute MI. **Conclusion-** An intake of folic acid 5mg/day for three months resulted in significant reduction of homocysteine, blood pressure, low density lipoprotein & total cholesterol.

**Keywords** – homocysteine, folic acid, cardiovascular diseases, hypertension.

### INTRODUCTION:

Cardiovascular disease accounts for about 30 % mortality worldwide. Efforts should be made to decrease the disease burden and longevity of life. An adequate screening & prevention of the disease should be focussed on. Medical management of the situation with polypill could decrease the risk of CVD in patients at risk. The major risk factors for CVD include diabetes,

hypertension, hypercholesterolemia and cigarette smoking, which lead to atherosclerosis & high serum levels of homocysteine. Homocysteine alone stands as an independent risk factor for CVD. (1) Hyperhomocysteinemia can be caused due to genetic predisposition, renal insufficiency, certain drugs, or nutritional deficiencies of folate, vitamin B6, or vitamin B12.

Homocysteine, a sulfur-containing amino acid is produced during the metabolism of methionine, an essential amino acid derived from dietary protein. Metabolism of Homocysteine occurs through two vitamin-dependent pathways viz. remethylation (requiring folate and vitamin B12), which converts homocysteine back to methionine and transulfuration (pathway requiring vitamin B12), which converts homocysteine to cysteine and taurine. (2)

Folic acid, a water soluble B vitamin, has been demonstrated to have efficacy in improving various disorders through proper diet supplementation. It acts through four mechanisms in atherosclerosis: (i) reducing homocysteine level & ensuring optimal functioning of the methylation cycle, (ii) antioxidant effects, (iii) interacting with enzyme endothelial nitric oxide synthase & (iv) affecting cofactor bioavailability of nitric oxide.(3)

Thus, the present prospective study was aimed to evaluate the effect of folic acid (5mg) supplementation for five months on serum homocysteine levels in patients suffering from cardiovascular diseases.

## MATERIAL & METHODS

The present prospective randomized controlled clinical trial was conducted in the Department of Medicine of our tertiary care hospital from April 2015 to Jan 2016. The study recruited 50

patients who were admitted with the chief complaints of chest pain aged > 40 yrs of age as the test group. Patients with renal failure, hepatic failure, pregnancy, hypothyroidism and epilepsy were excluded from the study. Apparently healthy individuals were taken as the control group. MI was confirmed using a standard 12-lead ECG. The Study was approved by the institutional ethical committee & written informed consent was sought from the study participants.

Study subjects in the test group were administered 5 mg folic acid per day orally for a period of five months in addition to their drug regimen. Venous blood samples were collected after overnight fasting at baseline and after 5 months for the assessment of Serum total homocysteine, serum total glyceride (TG), total cholesterol (TC), and high density lipoprotein (HDL). Normal serum homocysteine reference values for an adult lie between 5 and 15  $\mu\text{mol/L}$ .  
Statistical analysis

The tabulated data was statistically analyzed using SPSS version 22.0 for Windows (IBM Corp,India). Quantitative data are presented as mean  $\pm$  SD or proportions. Intergroup comparisons were made using Student's paired t-test. P-value 0.05 at a 90% confidence interval was considered to be statistically significant. Values were expressed as number (n) and percentage (%).

## RESULTS

In the present study, age & gender controlled matches were recruited.(Table 1) The serum levels of homocysteine were significantly higher in the test group than control group at baseline ( $p<0.005$ ). (Table 1) In the test group, Serum homocysteine level observed a statistically significant reduction from baseline at 5 months after the administration of folic acid ( $p<0.005$ ). This reduction was observed in all the study subjects whether they were smokers/nonsmokers, alcoholics/nonalcoholics or suffered from angina or acute MI . In the test group, TC, TG, LDL, SBP, DBP and serum homocysteine levels in CVD patients group were statistically higher when compared with the control group. (Table 2)

**Table 1 Sociodemographic details of study subjects**

Parameters	Test Group (n=50) (Mean $\pm$ SD)	Control Group (n=50) (Mean $\pm$ SD)
Age (yrs)	51.6 $\pm$ 5.1	48.4 $\pm$ 4.79
BMI	27.69 $\pm$ 2.44	23.75 $\pm$ 1.83
Men	65%	62%
Women	35%	38%
Smokers	21%	15%
Alcoholics	74%	68%
Clinical condition		-
Angina	74%	
MI	26%	

**Table 2 Levels of different parameters at baseline and at 5 months**

	Test Group (n=50) (Mean $\pm$ SD)		Control Group (n=50) (Mean $\pm$ SD)	P value
	At baseline	At 5 months		
Serum homocysteine ( $\mu$ mol/L)	23.61 $\pm$ 2.73	14.74 $\pm$ 3.5	14.7 $\pm$ 1.28	<0.005
TC	220 $\pm$ 12.46	194 $\pm$ 14.23	155.4 $\pm$ 2.45	<0.05
TG	219.3 $\pm$ 18.54	202 $\pm$ 14.72	178 $\pm$ 20.46	<0.05
HDL	42.3 $\pm$ 3.7	44.2 $\pm$ 4.1	43.7 $\pm$ 5.3	<0.05
LDL	130.45 $\pm$ 14.2	89 $\pm$ 22.4	84.2 $\pm$ 20.4	<0.05
SBP	153 $\pm$ 5.02	132.6 $\pm$ 4.31	132.4 $\pm$ 3.4	<0.05
DBP	94 $\pm$ 3.4	86 $\pm$ 2.1	87.3 $\pm$ 2.4	<0.05

## DISCUSSION

Plasma homocysteine has been proven to be a novel & independent risk factor for CVD in populations worldwide. Elevated homocysteine concentrations have been observed to be related to reduced vitamin B12 and folate levels. Thus, supplementation of these nutrients in the diet may lead to decreased CVD. (4) In the present

study, test group parameters revealed statistically significantly higher serum homocysteine levels as compared to the control group at baseline( $p < 0.005$ ). The levels of serum homocysteine did not show any difference in men & women. Previous studies by Brilakis et al observed hyperhomocysteinemia to be a risk factor for premature CAD in men but not so in women.(5) Study by F Jalali et al 2007, noted higher serum homocysteine levels in men as compared to women at baseline. Alon Schaffer et al 2014 conducted a large prospective cohort including 3056 patients undergoing coronary angiography. The study concluded higher homocysteine levels which were associated with age, male gender, hypertension, previous CVA/MI ( $p < 0.001$ ). (6)

In the present study, test group observed serum homocysteine levels significantly reduced after the completion of 5 months of folic acid treatment( $p < 0.005$ ). Accordingly, Daly et al 2002 conducted a study on administering folic acid supplementation in premenopausal women & observed reductions in serum homocysteine levels. (7) Schorah et al found that in cereals fortified with 200  $\mu\text{g}$  of folic acid observed a statistically significant reduction in plasma homocysteine in healthy volunteers. (8) Also, Wald et al. (9) and Rydlewicz et al 10 reported that a minimum of 400  $\mu\text{g}/\text{day}$  folic acid was necessary to bring about a notable reduction of plasma

homocysteine in patients with ischemic heart disease (9) or in the elderly.(10)

In the present study, in the test group, smokers were observed to have statistically significantly higher serum homocysteine levels as compared to nonsmokers( $p < 0.05$ ). Similarly, studies by O'Callaghan P 2002 11 & S. Ganeshan 2014 (12) produced the same results. Nicotine and carbon monoxide present in smoke cause tachycardia, hypertension & vasoconstriction of blood vessels producing direct endothelial damage. Also, it has a significant effect on platelet aggregation, plasma viscosity and fibrinogen levels.(11) Vitamin B, folic acid, vitamin B6 and vitamin B12 act as cofactors (vitamins B6 and B12) or co-substrate (folate) for the enzymes which control homocysteine metabolism. Smokers have been shown to have low levels of these cofactors, which affects the metabolism of homocysteine & raises its levels.(13)

In the present study, study subjects with chronic alcoholism were observed to have statistically significantly higher serum homocysteine levels as compared to nonalcoholics( $p < 0.05$ ). Similarly, a study by S. Ganeshan et al 2014 demonstrated the same results. The etiology behind it could be attributed to low dietary intake, poor absorption, reduced hepatic uptake & increased excretion of folate in urine.(12)

In the present study, TG, TC, HDL, SBP & DBP levels in the test group showed statistically

significant reductions at 5 months. Similarly, a study by S. Ganeshan et al 2014<sup>12</sup> observed the same results .

Bhargava S 2012 concluded that 5 mg of folate alone or in combination with folate(1.5 mg) and cobalamin (500 mg) are equally effective in the reduction of homocysteine. Food fortification is a cheap & easily available method to benefit the human population. Thus, policymakers in our country should evaluate this food fortification, to correct nutritional deficiencies as well as decrease the risk for CVD & other vascular diseases to reduce the disease burden.**(14)**

## CONCLUSION

Thus the present study concluded that an intake of folic acid 5mg/day for three months resulted in a significant reduction of homocysteine, blood pressure, low density lipoprotein & total cholesterol. Homocysteine levels should be assessed in patients suffering from varied diseases for an early detection & management from hypertension, hyperlipidemia, CVD, Alzheimer's disease.

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