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Research Article

EFFECT OF FOLIC ACID, PYRIDOXINE AND CYANOCOBALAMIN IN REDUCING THE ELEVATED LEVEL OF HOMOCYSTEINE IN ADVANCE CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE

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ABSTRACT

Homocysteine is an amino acid that is produced by the body and it can be converted into methionine or cysteine with the aid of B-vitamins and tetrahydrofolate. Renal function is a major determinant of plasma homocysteine concentration, and patients with chronic renal failure have severe hyperhomocysteinemia. The aim of study was to determine the effect of high doses of folic acid, vitamin B_6 and B_{12} to reduce the homocysteine levels in chronic kidney disease patients. In present study, 60 renal failure patients fulfilled study criteria. These 60 patients, were divided into two groups of which 30 were selected into control and 30 were recruited in sample. The average of Hcy levels before starting treatment was obtained 31.14 umol/L. After treating patient with folic acid, vitamin B_6 and B_{12} for a period of 3 months the average serum homocysteine level was measured and resulted 27.43 umol/L. Our study showed decrease and/or improve in average level of serum homocysteine among end stage renal failure and chronic kidney disease patients who have been received folic acid and vitamin B_6 and B_{12} supplements, compared with controls. Risks due to increased homocysteine causes heart disease, stroke, peripheral vascular disease, diabetes. Our study concludes that high doses of folic acid, vitamin B_6 and B_{12} treatment has improved or decreased the levels of Hcy in patients with renal failure, which in turn has reduce the risk of cardiovascular complications. This will improve quality of life of patients and decreases the mortality rate due to cardiovascular disorders.

Keywords: Advance Chronic Kidney Disease, End-Stage Renal Disease, Hyperhomocysteinemia, Folic Acid, Cyanocobalamin

INTRODUCTION

Homocysteine (Hcy) is an amino acid in the blood for digesting of dietary protein. Increased levels of homocysteine are related to a higher risk of coronary heart disease, stroke and peripheral vascular disease (fatty deposits in peripheral arteries) by damaging the inner lining of arteries and promoting blood clots. Hcy levels in blood plasma predicts risk of death from cardiovascular disease in older people. Raised levels of homocysteine are also linked to Alzheimer's, dementia and declining memory. Homocysteine therefore shown to play a crucial role as a key marker for disease development determining longevity and health throughout a life. [1, 2, 3] Hyperhomocysteinemia is a medical condition characterized by an abnormally high level of homocysteine in the blood which is classified according to fasting plasma Hcy levels, as moderate (fasting plasma Hcy levels 30-100umol/L) or severe (fasting plasma Hcy levels >100 umol/L.[4] In 1969, MC-Cully, proposed that high plasma total homocysteine concentration caused severe atherothrombotic disease and death in adolescents with homocystinuria.[5] Renal function is a major determinant of plasma homocysteine concentration, and patients with chronic renal failure have severe hyperhomocysteinemia.[6] It has been suggested that homocysteine is a cause of cardiovascular disease in renal failure.[7] Treatment with folic acid reduces plasma homocysteine in subjects with normal renal function by 30%.[8] Folic acid also lowers plasma homocysteine in patients with chronic renal failure .[9] Total homocysteine (tHcy) is a metabolite of the essential amino acid methionine. Hcy production is dependent on s-adenosyl-methionine (SAM) that is responsible for multiple intracellular methylation reactions is S-adenosyl homocysteine(SAH), which is hydrolysed to Hcy. When there is an excess of methionine, Hcy is metabolized via the pathway of trans sulfurylation, producing cystathionine and cysteine in turn. The responsible enzyme for the transformation of Hcy to cystathionine is cystathionine b-synthase (CBS) that requires vitamin B_6 as an essential co-factor.[10] Cystathionine-β-synthase, also known as CBS, is an enzyme that in humans is encoded by the CBS gene which the most common locus for mutations associated with homocystinuria.[11] Patients with chronic kidney disease or end-stage renal disease have higher homocysteine levels. They have extensive vascular disease, with estimates of annual mortality as high as 20%.[4] Patients with end-stage renal disease have mildly to moderately elevated plasma total Hcy concentrations, typically in the range of 20 to 80 gmol/L.[12] If a person ingests lots of protein, and there is not enough folic acid, vitamin B_6 and vitamin B_{12} available to help digest it, homocysteine levels can build up in the blood stream. Indeed, studies have shown that oral folic acid supplements are effective in bringing homocysteine levels down. The complex metabolism of homocysteine within the body is highly dependent on vitamin derived cofactors, and deficiencies in vitamin B_{12}, folic acid and vitamin B_6 are associated with hyperhomocysteinaemia. [2, 13] The best way to prevent hyperhomocysteinemia is to eat foods which contain B_6, B_9, B_{12} and taurine, such as potatoes, greens, beans, and fish. The only natural sources of B_{12} are from animal products. It is also found in fortified breakfast cereals and enriched soy or rice milk. Supplementation with pyridoxine, folic acid, B_{12}, or

trimethylglycine (TMG or betaine) reduces the concentration of homocysteine in the bloodstream.[14]

MATERIALS AND METHODS

Procedure

A prospective interventional study was conducted in the nephrology department at Kempegowda Institute of Medical Science and Research Centre (KIMS) hospital and research centre from November 2014 to October 2015. The study protocol was approved by the hospital's research ethics committee and all participants gave written informed consent. Adults patients of either sex, aged ≥ 30 years and above were enrolled for the study.

Patients were recruited after inclusion criteria have been satisfied and after taking an informed consent. The sources used for collecting data are patient case sheets, medications orders, laboratory reports. Homocysteine level is screened in 60 patients (divided into equal participants number of sample and control group) who are diagnosed to have an advanced chronic kidney disease by the Nephrologist. Then the blood analysis was done for Hcy by drawing 2 ml of blood from the recruited patient with the help of nursing staff and stored in ethylene diamine tetra acetic acid (EDTA) tubes (using EDTA or heparin to prevent coagulation) and then data has been collected and retrieved into the data collection form, the same is informed to the nephrologist. Pre-dialysis blood samples were obtained just prior to starting folic acid, vitamin B_6 and vitamin B_{12} and after 3 months continuous treatment of participants, blood sample has been collected by same procedure from sample and control group. The normal ranges of homocysteine for this assay are range from 5 to 15µmol/L.

Inclusion Criteria

1. Patients who were diagnosed to have advanced chronic kidney disease (ACKD) and end stage renal disease (ESRD) admitted to Nephrology Unit, KIMS hospital and Research Centre.
2. Patients of either sex, aged ≥ 30 years and above.

Exclusion Criteria

1. Patients with cardiovascular complications with CKD.
2. Patients with Drug Induced Renal Failure.
3. Patients who refuse to give the consent form.

Table 1: Sex Distribution of Patients with Renal Failure

Sex	Control	Sample
Male	27	25
Female	03	05

Table 2: Age Distribution of Patients with Renal Failure

Age	Control	Sample
31-40	15	04
41-50	08	11
51-60	05	07
61-70	02	08
> 70 year	00	00

Table 3: Homocysteine Levels before Treatment

Sr.No	Age	Sex	HcY* levels (umol/L)	Sr.No	Age	Sex	HcY levels (umol/L)
Sample							
1	46	F	58.68	**16**	66	M	33
2	45	M	9.54	**17**	57	M	48
3	64	M	27.49	**18**	39	M	12.83
4	56	M	65	**19**	47	M	20.12
5	48	M	57.17	**20**	53	F	27.55
6	48	M	12.47	**21**	58	M	34.02
7	64	M	13.21	**22**	64	M	44.51
8	38	M	54.34	**23**	50	M	28.2
9	64	M	47.32	**24**	63	M	42
10	52	M	15.45	**25**	67	F	25.81
11	47	M	17.03	**26**	33	M	32.88
12	50	F	26	**27**	48	M	12.7
13	62	F	29.32	**28**	60	M	39.02
14	52	M	43	**29**	37	M	10.93
15	41	M	27	**30**	44	M	19.83
Control							
1	50	M	15.54	**16**	37	M	32.31
2	44	M	11.2	**17**	34	M	30
3	62	M	12.47	**18**	48	M	24.2
4	28	M	10.3	**19**	50	M	26.1
5	28	M	29.43	**20**	48	F	30.01
6	54	M	25.31	**21**	32	M	22.23
7	31	M	30	**22**	40	M	18
8	36	M	9.3	**23**	64	M	32.11
9	55	M	11.2	**24**	35	M	20
10	48	M	16.43	**25**	28	F	39.81
11	50	M	42.31	**26**	46	M	34.32
12	32	M	25	**27**	51	M	12
13	29	F	14.3	**28**	60	M	30.18
14	34	M	20.11	**29**	37	M	31.19
15	51	M	23.02	**30**	32	M	28.2

*Homocysteine

Table 4: Homocysteine Levels after Treatment

Sr.No	Age	Sex	HcY* levels (umol/L)	Sr.No	Age	Sex	HcY levels (umol/L)
Sample							
1	46	F	36.21	**16**	66	M	33.01
2	45	M	12.23	**17**	57	M	41.32
3	64	M	25.81	**18**	39	M	10.01
4	56	M	48.43	**19**	47	M	18.91
5	48	M	44.16	**20**	53	F	27.9
6	48	M	10.64	**21**	58	M	30
7	64	M	10.21	**22**	64	M	42.12
8	38	M	46.5	**23**	50	M	28.22
9	64	M	36.7	**24**	63	M	41.22
10	52	M	13.23	**25**	67	F	23.06
11	47	M	15.54	**26**	33	M	30.01
12	50	F	26.02	**27**	48	M	11.88
13	62	F	28.83	**28**	60	M	39.03
14	52	M	40.02	**29**	37	M	10.74
15	41	M	24.08	**30**	44	M	17.07
Control							
1	50	M	16.15	**16**	37	M	31
2	44	M	10.91	**17**	34	M	27.71
3	62	M	12.36	**18**	48	M	24
4	28	M	12.3	**19**	50	M	21.11
5	28	M	32.43	**20**	48	M	20.13
6	54	M	26.4	**21**	32	F	16.88
7	31	M	EXPIRED	**22**	40	M	12.8
8	36	M	8.9	**23**	64	M	30.22
9	55	M	10.8	**24**	35	M	17.72
10	48	M	17.56	**25**	28	M	20.12
11	50	M	40	**26**	46	F	32.4
12	32	M	24.51	**27**	51	M	8.9
13	29	M	10.08	**28**	60	M	29.7
14	34	F	18.91	**29**	37	M	30
15	51	M	22.37	**30**	32	M	28.7

* Homocysteine

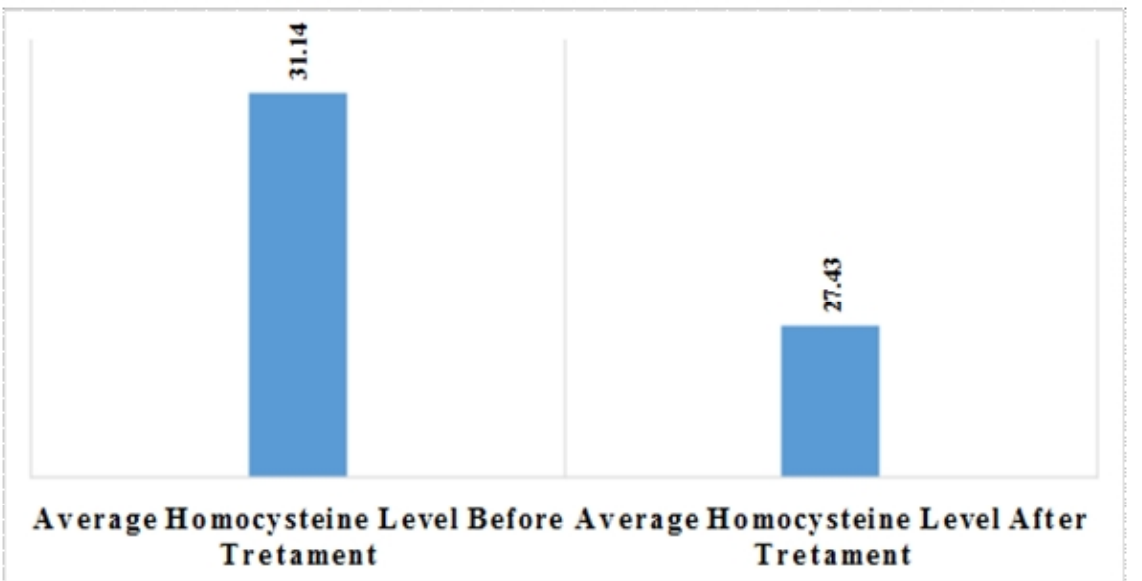


Figure 1: Comparison of Homocysteine Levels before and after Starting the Treatment in Renal Failure Patients.

RESULTS

A total 60 patients with end stage renal disease and chronic kidney failure were selected during the period of study (6 months). These 60 patients, were divided into two groups of 30 members which include control and sample subjects. In control group out of all, 27 male and 3 are female. In sample there are 30 patients with renal failure out of which 25 are male and 5 female (Table 1). In control there are fifteen patients in the age group of 31-40 years whereas in sample there is only four patient. In control there is only eight patients in the age group of 41-50 years whereas in sample there are eleventh patients. In control there are five patients in the age group of 51-60 years whereas in sample there are seven patients. In control there are two patients in the age group of 61-70 years whereas in sample there are eight patients (Table 2). Table 3 and 4 show age, sex and homocysteine level of all sample and control patients before and after complete of treatment period (3 months) with folic acid, vitamin B_6 and vitamin B_{12}. Correlation of pre - homocysteine levels before starting the treatment and post - homocysteine levels after starting the treatment in renal failure patients shown in Figure 1.

DISCUSSION

Present study has been emphasized and justified the role and the benefit of using folic acid, vitamin B_6 and vitamin B_{12} for the treatment of hyperhomocysteinemia in patients with end stage renal failure and chronic kidney disease. In present study, we recruited about 60 renal failure patients with end stage renal failure and chronic kidney disease. These 60 patients, were divided into two groups of which 30 were recruited into control and another 30 participants were recruited in sample. In control there are 15 patients in the age group of 31-40 years whereas in sample there is only 4 patients. In sample group highest number of patients was observed age group 41-50 years. In both group there was no patient aged above 70 years. There were similar studies conducted by N.R robles et al., were they had forty six renal failure patients of which 25 males and 21 females. These patients were compared with the control groups with normal renal function (22 males and 13 women). Plasma homocysteine values were measured in both groups.[15]

The average homocysteine level before starting treatment was found to be 31.14 umol/L. After complete the period of treatment (3 months) the average of serum homocysteine level was obtained 27.43 umol/L. The study conducted by N Nand et al. on 100 CKD cases in tertiary care hospital for 6 months and the results showed that elevated homocysteine levels were reduced by folic acid and vitamin B_{12} therapy. [16] Our study resulted decrease in average of homocysteine level among end stage renal failure and chronic kidney disease patients who have been treated with folic acid and vitamin B_6 and B_{12} supplements, compared with controls.

Limitation

Study limitation should be noted for better interpretation. The study was done for a short term period of 6 months. Sample size is less for both control and standards group. Hence a longer term study with a larger group of patients can be carried out, as the treatment requires longer duration and more number of follow-ups. Recruitment of patients, convincing them for blood sample were difficult.

CONCLUSION

Our study concludes that high doses of folic acid, vitamin B_6 and B_{12} treatment has improved or decreased the levels of homocysteine in patients with renal failure, which in turn as reduce the risk of cardiovascular complications. This will improve the quality of life of patients and decreases the mortality rate due to cardiovascular disorders.

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