

HOMOCYSTEINE LEVELS IN CHRONIC KIDNEY DISEASE STAGE V / END STAGE RENAL DISEASE ON MAINTENANCE HEMODIALYSIS AND THEIR PROGNOSTIC VALUE IN VASCULAR DISEASES

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ABSTRACT: INTRODUCTION: Majority of patients with CKD stage V on maintenance hemodialysis have hyper homocysteinemia because of decreased excretion and loss of renal homocysteine metabolism. Homocysteine is a risk factor for vascular diseases. **AIMS AND OBJECTIVES OF THE STUDY:** To demonstrate hyper homocysteinemia in chronic kidney disease stage V on maintenance hemodialysis and to follow up these patients if they develop any vascular complications. **MATERIALS AND METHODS:** This study includes 30 patients with CKD stage V on maintenance hemodialysis with age variation between 35-72 years, and in these patients fasting plasma homocysteine levels was assayed. These patients were followed up for 2 years for vascular complications. **CONCLUSION:** Out of 30 patients of CKD stage V on maintenance hemodialysis, 25 patients (83.33%) have elevated homocysteine Levels. Majority of these patients, homocysteine levels are within moderate range (30-100µmol/l). On follow up no patient developed any major vascular complications such as symptomatic IHD, neurological deficits or any symptomatic peripheral vascular diseases.

KEYWORDS: Homocysteine, Hemodialysis, CKD, Cerebrovascular diseases, Cardiovascular diseases.

INTRODUCTION: Homocysteine is a sulphur containing amino acid which is produced during metabolism of the essential amino acid methionine.

Impaired kidney function leads to increased plasma homocysteine levels by 2 to 3 folds by following mechanisms:

1. Decreased excretion.
2. Decreased re methylation of homocysteine to methionine in tubule interstitium of kidney.^[1]

Direct correlation exists between increasing creatinine and homocysteine levels.^[2] Hyper homocysteinemia is more prevalent in the hemodialysis patient than continuous ambulatory peritoneal dialysis, probably because of removal of water soluble vitamins such as B6, B12 during dialysis.^[3] Thus majority of end stage renal disease patients on hemodialysis are burdened by additional cardio vascular risk factors of hyper homocysteinemia.^[4,5] Thus hyper homocysteinemia in chronic kidney disease is mainly because of decreased excretion and loss of renal homocysteine metabolism which normally accounts for 70% of daily elimination of homocysteine from plasma.

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High homocysteine levels are associated with vascular disease.^[6] Such as;

- Atherosclerosis.^[7]
- Cardiovascular diseases.^[8]
- Cerebrovascular diseases.^[9,10]

AIMS AND OBJECTIVES OF THE STUDY: To demonstrate hyper homocysteinemia in chronic kidney disease stage V on maintenance hemodialysis and to follow up these patients if they develop any vascular complications.

MATERIALS AND METHODS: Adult patient with chronic kidney disease stage V on maintenance hemodialysis presenting to the department of nephrology at Govt. General Hospital, Kurnool.

Study Type: Cross-sectioned study with follow up for 2 years for vascular complications.

Sample Size: 30.

Investigations done in my study;

1. Homocysteine levels estimation by FLUORESCENCE POLARIZATION IMMUNOASSAY.
2. Complete blood picture.
3. Blood urea.
4. Serum Creatinine.
5. Blood Sugar.
6. Lipid profile.
7. Thyroid function test.
8. Serum electrolytes.
9. Serum calcium, phosphorus, alkaline phosphates.
10. ECG.
11. Ultra sound abdomen.
12. Urine for albumin, sugar and deposits.
13. CT-Brain.
14. 2D Echo.
15. Doppler study of neck vessel.
16. Doppler study of lower limb vessel.

Inclusion Criteria: All patients with chronic kidney diseases stage V/ end stage renal disease on maintenance hemodialysis.

Exclusion Criteria:

1. Patients having previous history of IHD, CVD, PVD.
2. Patients not having any malignancies.
3. Patient on medications such as metformin, Methotrexate, Niacin, anticonvulsants.

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RESULTS:

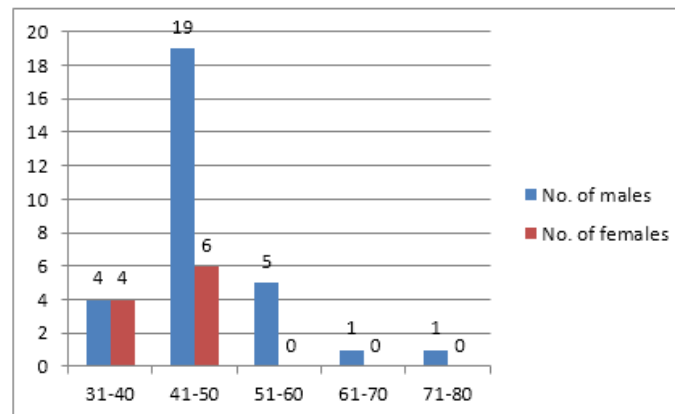
Patient age group	No. of Males	No. of Females	Total No. of Patients	Percentage
31-40	4	4	8	26
41-50	19	6	15	50
51-60	5	0	5	16.5
61-70	1	0	1	3.33
71-80	1	0	1	3.33

Table 1: Age distribution of cases

Mean=51.

Out of 30 patients 50% of the patient's age is within 41-50 years.

Graph 1: AGE DISTRIBUTION OF CASES



Sex	No. of patients	Percentage
Males	20	66.66
Females	10	33.33

Table 2: Sex distribution of cases

Male: Female ratio=2:1.

Grading of Homocysteine levels	No. of Male Patients	Percentage of Male Patients
Normal <15μmol/L	4	20
Moderate 15-30μmol/L	5	25
Intermediate 30-100 μmol/L	8	40
Severe >100μmol/L	3	15

Table 3: Grading of Homocysteine levels in Male patients & their percentages

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Majority (40%) of male patients with homocysteine levels are within intermediate range.

Grading of Homocysteine levels	No. of Female Patients	Percentage of Female Patients
Normal <15 μ mol/L	1	10
Moderate 15-30 μ mol/L	5	50
Intermediate 30-100 μ mol/L	4	40
Severe >100 μ mol/L	0	0

Table 4: Grading of Homocysteine levels in female patients & their percentages

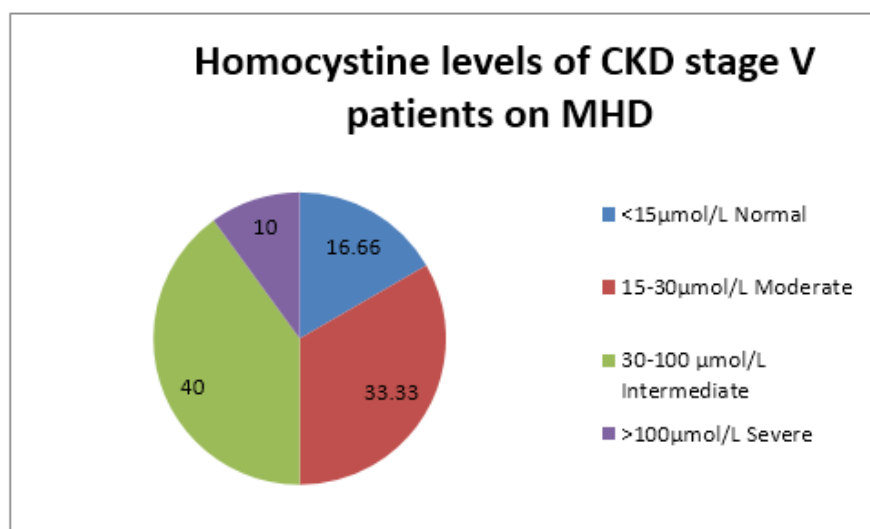
Majority (50%) of female patients with Homocysteine levels are within moderate range.

Hey levels of CKD stage V patients on MHD total No. of pt-30	Grading of Hyper homocysteinemia	Total no. of patients	Percentage
<15 μ mol/L	Normal	5	16.66
15-30 μ mol/L	Moderate	10	33.33
30-100 μ mol/L	Intermediate	12	40
>100 μ mol/L	Severe	3	10

Table 5: Grading of Homocysteine levels in total sample size & their percentages

- Percentage of patients with normal homocysteine levels-16.66%.
- Percentage of patients with hyperhomocysteinemia-83.33%.
- Out of this majority (12 in number) of patients of patient Homocysteine levels are within intermediate range.

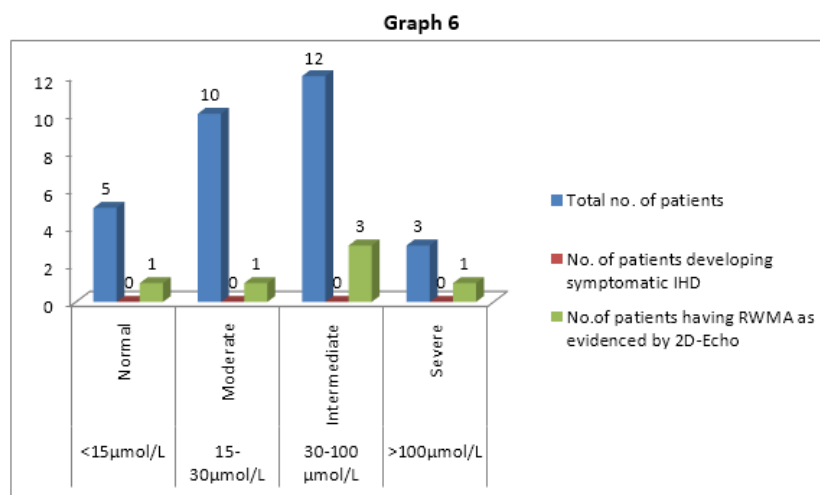
Graph 5



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Homocysteine levels of CKD stage V patients on MHD	Grading of Hyper homocysteinemia	Total no. of patients	No. of patients developing symptomatic IHD	No. of patients having RWMA as evidenced by 2D-Echo
<15 μ mol/L	Normal	5	0	1
15-30 μ mol/L	Moderate	10	0	1
30-100 μ mol/L	Intermediate	12	0	3
>100 μ mol/L	Severe	3	0	1

Table 6: CVS changes in CKD patients according to grading of Homocysteine



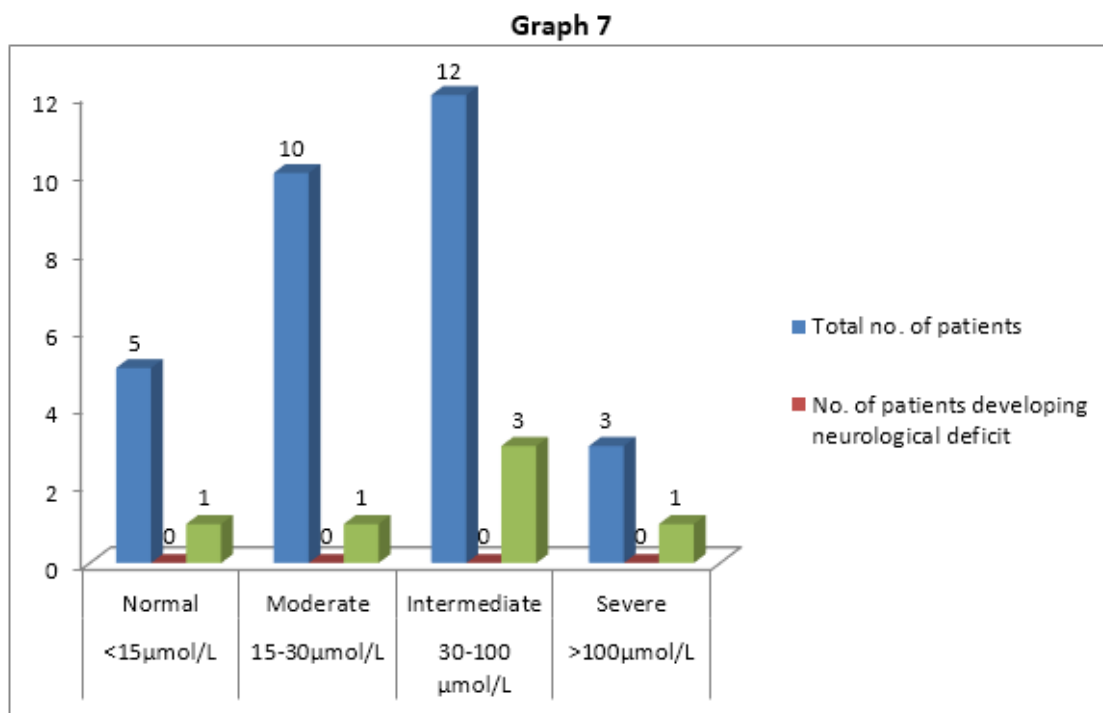
No. of patients developed symptomatic IHD and 2D echo evidence of RWMA in moderate, intermediate severe hyper Homocysteinemia.

- Percentage of patients developed symptomatic IHD-nil.
- Percentage of patients with normal Hey level developed RWMA-20%.
- Percentage of patients with hyper Homocysteinemia developed RWMA-20%.
- No significant difference made out between normal or hyper Homocysteinemia patients.

Homocysteine levels of CKD stage V patients on MHD	Grading of Hyper Homocysteinemia	Total no. of Patients	No. of patients developing neurological deficit	No. of patients Developed lacunar infarcts in CT brain S/O small vessel stroke
<15 μ mol/L	Normal	5	0	1
15-30 μ mol/L	Moderate	10	0	2
30-100 μ mol/L	Intermediate	12	0	3
>100 μ mol/L	Severe	3	0	1

Table 7: CNS changes in CKD patients according to grading of Homocysteine

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No. of patients developed neurological deficit and lacunar infarcts in CT brain S/O small vessel stroke in normal and moderate, intermediate severe hyper Homocysteinemia.

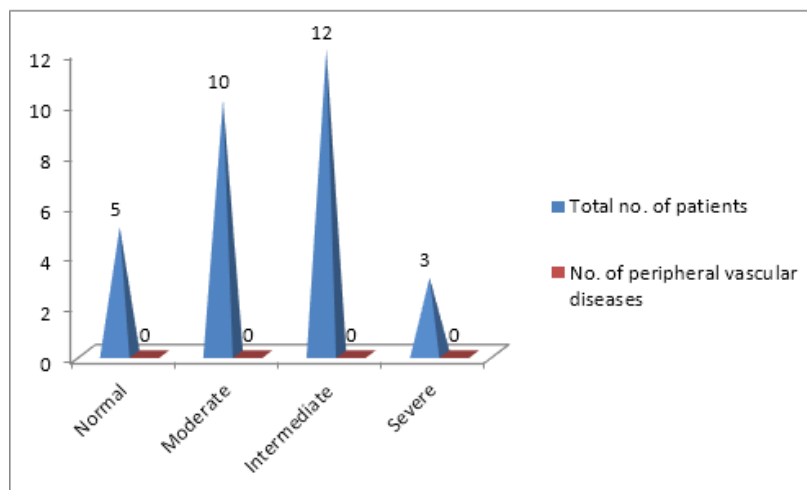
- Percentage of patients developed neurological deficit –nil.
- Percentage of patients with normal Homocysteine level developed lacunar infarcts-20%.
- Percentage of patients with hyper Homocysteinemia developed lacunar infarcts -24%.
- No significant difference made out between normal or hyper Homocysteinemia patients.

Homocysteine levels of CKD stage V patients on MHD	Grading of Hyper Homocysteinemia	Total no. of Patients	No. of Peripheral Vascular diseases
<15μmol/L	Normal	5	0
15-30μmol/L	Moderate	10	0
30-100 μmol/L	Intermediate	12	0
>100μmol/L	Severe	3	0

Table 8: Peripheral vascular diseases in CKD patients according to grading of Homocysteine

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Graph 8



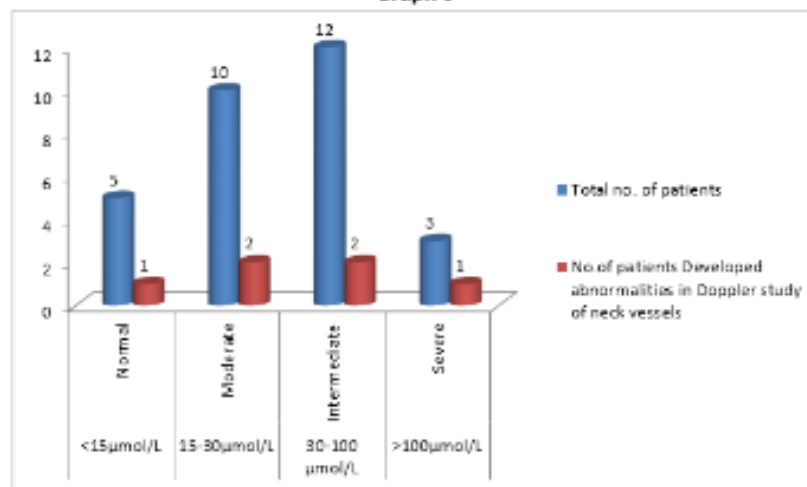
No. of patients developing peripheral vascular diseases in patients with moderate, intermediate severe hyper Homocysteinemia.

Percent of patients developing peripheral vascular disease – nil.

Homocysteine levels of CKD stage V patients on MHD	Grading of Hyper Homocysteinemia	Total no. of patients	No. of Patients Developed abnormalities in Doppler study of neck vessels
<15µmol/L	Normal	5	1
15-30µmol/L	Moderate	10	2
30-100 µmol/L	Intermediate	12	2
>100µmol/L	Severe	3	1

Table 9: Abnormalities in Doppler study in CKD patients according to grading of Homocysteine

Graph 9



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No. of patients developed abnormalities in Doppler study of neck vessels normal and moderate, intermediate severe hyper Homocysteinemia.

- Percentage of patients with normal Homocysteine level developed abnormalities in Doppler study of neck vessels -20%.
- Percentage of patients with hyper Homocysteinemia developed abnormalities in Doppler study of neck vessels -20%.
- No significant difference made out between normal or hyper Homocysteinemia patients.

Patients Homocysteine value	No. of patients with abnormal Echo findings present	No. of patients with abnormal Echo findings absent	Total no. of patients
Normal <15µmol/L	1	4	5
Elevated >15-30µmol/L	5	20	25
Total	6	24	30

Table 10: Echo findings in patients with normal & hyper Homocysteinemia

Yates corrected X^2 : 0.37.

df=1.

2 tailed P=0.54: NS (Non-Significant).

Patients Homocysteine value	No. of patients with abnormal CT findings present	No. of patients with abnormal CT findings absent	Total no. of Patients
Normal <15µmol/L	1	4	5
Elevated >15-30µmol/L	6	19	25
Total	7	23	30

Table 11: CT findings in patients with normal & hyper Homocysteinemia

Yates corrected X^2 :0.14.

df=1.

2 tailed P=0.69: NS (Non-Significant).

Patients Homocysteine value	No. of patients with abnormal carotid Doppler findings present	No. of patients with abnormal carotid Doppler findings absent	Total no. of patients
Normal <15µmol/L	1	4	5
Elevated >15-30µmol/L	5	20	25
Total	6	24	30

Table 12: Carotid Doppler findings in patients with normal & hyper Homocysteinemia

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Yates corrected X^2 :0.37.

df=1.

2 tailed P=0.54: NS (Non-Significant).

DISCUSSION: Fasting plasma Homocysteine levels were estimated in 30 patients of which 20 were males & 10 were females with CKD- Stage V on maintenance hemodialysis, age varying between 35-72 years. Majority (50%) of patient's age within 41-50 years. These patients were followed up for 2 years for evaluation of any vascular complications.

According to plasma Homocysteine levels these patients were graded as;

1. Normal $<15\mu\text{mol/l}$.
2. Moderate $15-30\mu\text{mol/l}$.
3. Intermediate $30-100\mu\text{mol/l}$.
4. Severe $>100\mu\text{mol/l}$.

Out of 30 patients 25 patients (83.33%) have elevated Homocysteine levels & majority of patients with Homocysteine values are in Intermediate range i.e. $30-100\mu\text{mol/l}$.

On follow up of these 30 patients no patient developed any major vascular complication such as symptomatic ischemic heart disease or neurological deficits or any symptomatic peripheral vascular disease. On observation there is no significant difference in occurrence of major vascular complications in hyper homocysteinemia when compared to normal homocysteinemia. And in the same follow up these patients have underwent some investigations, which show abnormalities like RWMA in 2D Echo, changes suggestive of ischemic in ECG, Lacunar infarcts in CT-Brain, mild atherosclerotic changes without any significant block in Doppler study of neck vessels.

From all the above observations finally the patients in the study were divided into 2 groups;

1. Normal homocysteine level patients ($<15\mu\text{mol/l}$) - 5 in no.
2. Hyper homocysteinemic patients ($>15\mu\text{mol/l}$) - 25 in no.

Among these two groups P value is calculated for 2 variables such as abnormal findings present or absent in 2D Echo, CT-Brain Doppler study of neck vessels which shows non-significance.

From the above discussion it is concluded that majority of patients with CKD stage V on maintenance hemodialysis have elevated homocysteine levels. 40% of these patients homocysteine values are within intermediate range i.e. $30-100\mu\text{mol/l}$. but these CKD patients with hyper homocysteinemia does not develop any major vascular complications except for minor morbidity when compared to normal homocysteine level patients.

References which shows non-significant relationship between homocysteine and vascular complications;

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1. In a case –control study, conducted in Care Hospital, Hyderabad.^[11] Study concluded that there is no statistically significant difference in plasma homocysteine levels between controls and cases with coronary artery disease.
2. Another study conducted Madras Diabetic Research Foundation, Chennai.^[12] They concluded that elevated serum homocysteine levels are not associated with coronary artery.
3. The utility of homocysteine in predicting risk for artherothrombotic vascular disease has been evaluated in several observational studies in a large number of patients. These studies show that the overall risk for vascular disease is small, with prospective, longitudinal studies reporting a weaker association between homocysteine and atherothrombotic vascular disease compared to retrospective case-control and cross-sectional studies. Furthermore, randomized controlled trials of homocysteine-lowering therapy have failed to prove a causal relationship. On the basis of these results, there is currently insufficiencent evidence to recommend routine screening and treatment of elevated homocysteine concentrations with folic acid and other vitamins to prevent atherothrombotic vascular disease.^[13]
4. The study conducted in Department Nutrition National Public Health Institute, Helsinki, Finland.^[14] There was also no significant association between homocysteine and atherosclerotic disease, myocardial infarction or stoke in logistic regression analysis. The results of this prospective population based study do not support the hypotheses that serum homocysteine is a risk factors for atherosclerotic disease.

CONCLUSION: From the above discussion.

1. It is concluded that majority 83.33% of patients with CKD stage V on maintenance hemodialysis have elevated homocysteine levels. 40% of these patients homocysteine values are within intermediate range i.e. 30-100 μ mol/l.
2. But these CKD patients with hyper homocysteinemia did not develop any major vascular complications except for minor morbidity when compared to normal homocysteine level patients. The above study suggests a lack of association between hyper homocysteinemia and vascular disease in patients with CKD stage V on maintenance hemodialysis.
3. The results however must be interpreted with caution due to limitation of the study firstly, the sample size was very small secondly we did not adjust for other cardiovascular risk factors again due to small sample size thirdly the duration of study is small i.e. 2 years only. Hence larger studies with longer duration of follow up needs to be done for further confirmation.

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