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Original research article

HOMOCYSTEINE LEVEL AS AN INDICATOR OF CARDIOVASCULAR MORBIDITY IN CHRONIC KIDNEY DISEASE

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Abstract

Background and Objectives: Chronic kidney disease (CKD) is a progressive, life threatening disease affecting more than $1/10^{th}$ of the worldwide population. Hyperhomocysteinemia (Hhcy), which is an independent predictor of cardiovascular disease (CVD), occurs in 85% of patients with CKD due to impaired renal metabolism and reduced excretion. The major cause of mortality in patients with chronic renal disease is cardiovascular causes, which may be reduced by lowering the homocysteine levels by folic acid supplementation.

Methods: 60 CKD patients who attended the OPD and wards of Gayatri Vidya Parishad Institute of Healthcare & Medical Technology (GVPIHC&MT) Hospital, Visakhapatnam, were identified and written informed consent was taken. Plasma homocysteine levels, ECG, blood sugars, renal function tests (RFT), GFR calculation, liver function tests (LFT) and complete hemogram were performed as part of the study. Patients with acute kidney injury, chronic smoking or alcohol consumption, preexisting cardiovascular disease, hepatic disease, diabetics and recently dialysed were excluded from the study. The accepted threshold for normal plasma homocysteine was 15 umol/litre or less.

Results: 42 of the 60 cases were men, and 18 were women. 39 patients were of age 41 to 60 and 21 were over 60. 7 patients had stage 3 CKD, 14 had stage 4 CKD and 39 patients had stage 5 CKD. 76.6% of the study population had hyperhomocysteinemia of whom 95% had abnormal ECGs. Patients with End Stage Renal Disease (ESRD) had

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higher incidence of Hhcy (85.55%).

Conclusion: Patients with CKD have high prevalence of Hhcy and increased cardiovascular risk, which can be reduced by folic acid supplementation.

Keywords: Hyperhomocysteinemia (Hhcy), chronic kidney disease (CKD), cardiovascular disease (CVD), folic acid supplementation

Introduction

More than 10% of the population are afflicted with CKD, with a total worldwide incidence of 843.6 million in 2017 [1]. Hyperhomocysteinemia (Hhcy), which is an independent predictor of cardiovascular disease (CVD), is seen in 85% of patients with CKD due to diminished renal metabolism and reduced excretion [2, 3]. CKD puts patients at increased risk of a wide variety of systemic diseases, of which CVD is the commonest contributor to morbidity and mortality in End Stage Renal Disease (ESRD) [4]. In India, one lakh cases get diagnosed with CKD each year, with a 38% rise in CKD related deaths between 2001-3 and 2010-13 [5].

Hyperhomocysteinemia which occurs in a majority (85%) of CKD patients leads to progression of the vascular damage which is already enhanced in CKD [4]. Homocysteine causes oxidative stress and interferes with vasodilator action of nitric oxide, leading to endothelial dysfunction, decreased vascular elasticity, increased hypertrophy and arterial stiffness [6, 7, 8]. Studies have pointed to an inverse relation between homocysteine levels and glomerular filtration rate [9]. A meta-analysis by Heinz *et al*. found a correlation between homocysteine levels and CVD mortality in ESRD patients, with a 5 mmol/L rise in homocysteine level resulting in a 9% increase in CVD mortality [10]. Studies are now being undertaken to ascertain whether a reduction in homocysteine levels in CKD patients can improve the cardiovascular outcomes [5]. The implication for conducting this research is to establish whether or not there is an association between poor renal function, increased homocysteine levels and CVD as data from such studies in this region are scarce.

Materials and Methods

A single-centered prospective study with observational design was carried out from June 2022 to December 2022 at GVPIHC&MT Hospital, Marikavalasa, Visakhapatnam. Institutional ethics committee clearance was obtained and informed consent was taken from the participating individuals. 60 patients with chronic kidney disease who attended the Medicine inpatient and outpatient departments and met the criteria for inclusion and exclusion were chosen for the study.

Inclusion criteria

Patients with known CKD having more than 3 months of the following.

1. GFR < 60 mL/min/1.73 m^2.
2. Deranged urea, creatinine, evidence of CKD on abdominal ultrasound.

Exclusion criteria: Patients with the following criteria.

1. Acute kidney injury.
2. Recent dialysis in the previous 2 days.

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3. History of smoking and chronic alcohol consumption.
4. Known chronic liver disease/underlying malignancies / diabetes mellitus.
5. Patients with preexisting cardiovascular disease.

Methodology

60 patients with known CKD (defined as GFR<60 mL/min/1.73 m^2 for > 3 months) [9], attending the medical inpatient/outpatient services were selected. Inclusion and exclusion criteria were reviewed, and informed consent was taken for suitable candidates. Social and anthropometric details such as age, gender, weight, height, and address were recorded. History pertaining to past medical history, renal replacement therapy, family history of CKD, comorbid conditions like diabetes mellitus, malignancies, chronic liver disease, CVD, and personal habits like smoking or consumption of alcohol was collected. Plasma homocysteine levels were measured using high performance chromatography with fluoroscein detection. Random blood sugar, RFT (urea, creatinine, serum electrolytes), GFR calculation (MDRD GFR Equation), complete hemogram, LFT, ECG, ultrasound abdomen and pelvis were performed. Calculations of percentage mean values, standard deviation, and standard error were performed on the data and outcomes were obtained by use of the T Test and the chi-square test. Statistical analysis was performed using the evaluation version of SPSS for Microsoft Windows 14. This allowed for accurate and reliable results.

Result

Table 1: Age distribution

Age (years)	Number of patients	Percentage
<20	1	2%
21-30	2	3%
31-40	6	10%
41-50	15	25%
51-60	24	40%
>60	12	20%

Table 2: Distribution of patients according to gender

Male	42	70%
Female	18	30%

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Table 3: Distribution of patients according to CKD stage

Stage of CKD	Number of patients	Percentage
0	0	0
1	0	0
2	0	0
3	7	12%
4	14	23%
5	39	65%

Table 4: Hyperhomocysteinemia

Sex	Total number	Increased homocysteine levels	Percentage of patients with hyperhomocysteinemia
Males	42	33	72%
Females	18	13	28%
Total	60	46	76.66%

Table 5: Elevated homocysteine level and stage of CKD

Stage of CKD	Number of patients	Normal homocysteine	Hyperhomocysteinemia (Hhcy)	Percentage of patients with hyperhomocysteinemia (Hhcy)
0	0	0	0	0
1	0	0	0	0
2	0	0	0	0
3	7	1	3	67.6%
4	14	4	9	74.72%
5	39	8	30	82.55%

Table 6: Normal and elevated homocysteine levels and ECG findings in CKD patients

ECG	Homocysteine	
	Normal	Increased
	12	40
Normal	12	4
Abnormal	0	40
Percentage of abnormal ECG	0%	95.7%

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Results and Discussion

Among the study population, a majority were found to be in the 51-60 age group (Table 1) with a male preponderance of 70% (Table 2). 12% of the patients had Stage 3 CKD, 23% had Stage 4 CKD and 65% had Stage 5 CKD (Table 3).

Hyperhomocysteinemia (Hhcy) is an important risk factor for atherosclerosis [11] and coronary artery disease [12] and has deleterious outcomes in CVD, cerebrovascular disease and nephropathy due to microvascular damage [13]. CKD is hugely prevalent in India and worldwide, with CVD being a leading cause of mortality and morbidity in patients with CKD. An observational study by S. Manoharan *et al*., in Tamil Nadu, detected hyperhomocysteinemia in 78% of CKD patients studied over 8 months [14]. Consistent with the findings of the above study, and other international research, 76.6% of the CKD patients in our study had hyperhomocysteinemia (Table 4). Participants had a male preponderance (70%), which was comparable with findings of Yu-Lin-Shih *et al*. [9] (Taiwan) and Yadav. V *et al*. [15] (Jaipur, India).

The stage of CKD was found to correlate with raised homocysteine levels, with higher incidence in CKD stages 3, 4 and 5 (Table 5). This aligns with the findings of Yu-Lin-Shih *et al*. [9]. ECG abnormalities were observed in 95.7% of subjects with Hhcy, highlighting the association between Hhcy and CVD (Table 6). A meta-analysis published in Homocysteine Studies Collaboration found an 11% lower risk of ischemic heart disease in patients with a lower homocysteine level. [16] Therefore, it is imperative for patients with CKD to take measures to reduce their homocysteine levels. In our study, every precaution was followed to filter out potential confounding factors, such as diabetes, malignancy, recent dialysis, chronic smoking and alcohol history, preexisting heart conditions and chronic liver disease.

Conclusions about hyperhomocysteinemia by gender could not be drawn with certainty due to disparities in sample size and sex proportion. Genetic variations impacting homocysteine level could not be ruled out. Vitamin B12, folic acid, or pyridoxine levels could not be assessed in all subjects due to funding constraints. Folic acid therapy reduces the CVD risk by 15% in ESRD patients. Optimum doses are under debate, ranging from 2.5 to 5mg folate taken thrice a week. Folate supplementation reduces, but does not normalize homocysteine in CKD patients [4].

Further research with a bigger sample size, assessment of vitamin levels, and genetic investigations are needed to better define the incidence and consequences of Hhcy in persons with CKD. A therapy plan aiming at decreasing homocysteine levels to reduce cardiovascular morbidity and mortality is required, as are large cohort studies to prove the precise association between the two.

Conclusion

Hyperhomocysteinemia (Hhcy) was observed in 76.6% of CKD patients. Hhcy was more prevalent in patients with CKD Stages 3, 4 and 5. Despite the fact that hyperhomocysteinemia was present in more than 75% of the patients studied, more research with a larger sample size and removing other risk variables is required to confirm these results.

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Conflict of interest

None.

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