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Original Research Article

Hyperhomocysteinemia in diabetic and/or hypertensive patients with CKD: A cross sectional study

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Abstract

Background & Objectives: Chronic kidney disease (CKD) is a commonly seen clinical condition resulting from different etiologies, diabetes and hypertension contributing to majority of CKD. Hyperhomocysteinemia is observed in CKD, which contributes to increased cardiovascular morbidity and mortalities according to many studies. Reduction of homocysteine level may help to decrease the cardiovascular morbidity and mortality which are leading cause of death in CKD patients.

Material and Methods: 90 patients with diabetes and/or hypertension, diagnosed as CKD with eGFR <90ml/min visiting the hospitals attached to BMCRI were chosen and their fasting plasma homocysteine level were measured. Patients less than 18 years age and had history of cerebral vascular disease, coagulopathy, Alzheimer's disease were excluded from the study. The data was summarized using mean, standard deviation for parametric data and median, interquartile range for non-parametric data and chi-square test was used for analyzing categorical variables.

Results: Hyperhomocysteinemia was observed in 63.33% of patients with CKD, majority of patients (26.3%) belonged to 50-59 years age group with a significant male (73.7%) preponderance in CKD with hyperhomocysteinemia group. Prevalence of Diabetes and Hypertension in CKD with hyperhomocysteinemia were 73.7% and 82.5% respectively and with a mean duration of Diabetes and Hypertension of 9.82 ± 7.073 years and 7.3 ± 6.545 years respectively. 12.3% patients in CKD with hyperhomocysteinemia were found to have underlying causes for CKD, among them around 57.1% of them had Chronic Interstitial Nephritis. Prevalence of hyperhomocysteinemia was more in end stages of CKD i.e. stage 3B (8.8%), stage 4 (15.8%) & stage 5 (75.4%). Homocysteine elevation was found in both CKD without dialysis and with intermittent hemodialysis.

Conclusion: Serum homocysteine levels appear to be closely associated with CKD and serum homocysteine levels are negatively associated with GFR. Thereby, serum homocysteine levels can be used as a marker of renal dysfunction in patients with diabetes and hypertension.

Keywords: Homocysteine, diabetes, hypertension

Introduction

Chronic kidney disease is defined as gradual loss of kidney functions and structure for more than 3 months. Chronic kidney disease (CKD) encompasses a spectrum of pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR) [1]. Hyperhomocysteinemia is defined as abnormal levels of homocysteine in the body of conventionally more than 15 micromoles/litre [2]. The rising prevalence of CKD has become a large public health problem in the world. A study done in

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the state of Karnataka found the prevalence of CKD to be at 6.3% [3]. The prevalence rates of Hyperhomocysteinemia are 5%-7% in the general population [4]. Hyperhomocysteinemia has been known to cause life threatening vascular complications affecting the cerebral artery [2]. But not many study has been made to prove its relationship with the development or progression of chronic kidney disease. Some studies have put forward a hypothesis of Hyperhomocysteinemia causing renal vascular injury and micro albuminuria and thereby causing progression of chronic kidney disease [5]. A study done by Nand N *et al*. published in Journal, Indian Academy of Clinical Medicine suggested that serum Homocysteine levels are elevated in patients of CKD and Folic acid, Vitamin B12 supplementation lowered homocysteine levels in such population [6].

It is shown that elevated serum homocysteine level is a predictor of accelerated decline in renal function and chronic kidney disease. The annual eGFR decline was observed to be 25% higher in subjects with elevated versus normal homocysteine levels [7]. Serum homocysteine levels are negatively associated with eGFR, thus responsible for the further progression of chronic kidney disease in the form of further decline in renal function and glomerular filtration rate by affecting the renal vasculature [8]. Hypertension, high blood glucose level, and dyslipidemia are classic risk factors for CVD. In addition, non-classic, residual risk factors for CVD have been reported [9]. For example, chronic Inflammation, oxidative stress, advanced glycation end-products, homocysteine, and uric acid are such risk factors.

It is believed that the decreased insulin secretory responsiveness, caused by the destructive production of reactive oxygen species (ROS) as a result of elevated homocysteine levels, leads to insulin resistance [10, 11]. It has also been suggested that in patients with insulin resistance, there is hepatic acceleration of glucocorticoid secretion that also leads to enhanced homocysteine catabolism and decreased plasma homocysteine levels [12].

Materials and Methodology

Patients with diabetes and/or hypertension with Chronic kidney disease with eGFR<90 attending to the OPD as well as in-patients with above criteria admitted to the Department of General Medicine of the hospitals attached to BMCRI during the study period of November 2019 to May 2021. Patients with history of cerebral vascular disease, coagulopathy, Alzheimer's disease and Deep Vein Thrombosis were excluded from the study. Statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 20. [IBM SPASS statistics (IBM corp. Armonk, NY, USA released 2011)], Descriptive statistics of the explanatory and outcome variables were calculated by mean, standard deviation for quantitative variables, frequency and proportions for qualitative variables and Inferential statistics like Chi-square test were applied to check the association for categorical variables.

Results

Out of the 90 CKD patients, number of patients presented with and without Hyperhomocysteinemia were 57 (63.3%) and 33 (36.6%). Among the CKD patients with Hyperhomocysteinemia majority of them belonged to 50-59 yrs age group (15 patients, 26.3%) followed by 12 patients (21.1%) in 40-49 yrs age group and least was in 20-29 yrs age group (5, 8.8%). Among the CKD patients without Hyperhomocysteinemia highest number of patients (10, 30.3%) of 40-49 yrs age group followed by 7 patients (21.2%) in 20-29 years age group. There were 42 (73.7%) male and 15 (26.3%) female patients and 20 (60.6%) male and 13 (39.4%) female patients in the CKD with and without hyperhomocysteinemia group respectively. The mean age was 50.65 ± 15.01 years in the CKD with Hyperhomocysteinemia group and 42.85 ± 13.83 years in the CKD without Hyperhomocysteinemia group (p=0.017). There was statistically significant difference in mean age between the study groups. In the CKD with Hyperhomocysteinemia group, 42 (73.7%) patients had Type 2 Diabetes Mellitus and 15 (26.3%) patients with no history of Type 2 Diabetes Mellitus. Out of 33 patients of CKD without Hyperhomocysteinemia group, 13 (39.4%) patients had Type 2 Diabetes Mellitus and 20 (60.6%) patients with no history of Type 2 Diabetes Mellitus. Statistical analysis of both the groups data shows there is

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statistically significant difference between the CKD with Hyperhomocysteinemia and CKD without Hyperhomocysteinemia groups with the p value 0.001. Patients with Hyperhomocysteinemia had Type 2 DM for 9.82 mean years of duration (9.82 ± 7.07) when compared to patients without Hyperhomocysteinemia had Type 2 Dm for 10.58 mean years of duration (10.58 ± 8.16) which was not statistically significant (p value-0.458). Out of 57 patients in CKD with Hyperhomocysteinemia group, 47 (82.5%) patients were found to have Hypertension with Hyperhomocysteinemia and 10 (17.5%) patients were not Hypertensive. Out of 33 patients in CKD without Hyperhomocysteinemia group, 26(78.8%) patients were found to have Hypertension and 7 (21.2%) patients were not Hypertensive (p value-0.668). Statistical analysis shows there is no significant difference in Hypertensive patients between CKD with Hyperhomocysteinemia group and CKD without Hyperhomocysteinemia group (p value-0.668). Patients with Hyperhomocysteinemia were hypertensive for 7.3 mean years of duration (7.3 ± 6.545) when compared to patients without Hyperhomocysteinemia, who were hypertensive for 5.87 mean years of duration (5.87 ± 6.206) which was not statistically significant (p value-0.364). Out of 57 patients in CKD with Hyperhomocysteinemia group, majority of patients did not have any underlying cause i.e. around 50 patients (87.7%) and around 7 patients (12.3%) had the specific underlying cause for Hyperhomocysteinemia. Out of 33 patients in CKD without Hyperhomocysteinemia group, majority of patients did not have any underlying cause i.e. around 27 patients (81.8%) and around 6 patients (18.2%) had the specific underlying cause for Hyperhomocysteinemia. Statistical analysis shows there is no significant difference in patients with underlying causes between CKD with Hyperhomocysteinemia group and CKD without Hyperhomocysteinemia group (p value-0.443). Out of 90 patients with chronic kidney disease, 13 patients had other underlying cause for Hyperhomocysteinemia i.e. 7 patients in CKD with Hyperhomocysteinemia and 6 patients in CKD without Hyperhomocysteinemia. Out of 7 patients with Hyperhomocysteinemia, majority patients (4, 57.1%) were suffering from Chronic Interstitial Nephritis followed by Ig A Nephropathy (1, 14.3%), medullary nephrocalcinosis x 1 year (1, 14.3%), Thrombotic microangiopathy x (1, 14.3%) and surprisingly there wasn't any patient having either Chronic Glomerulonephritis nor obstructive uropathy. In contrast to Hyperhomocysteinemia group, majority patients (2,33.3%) were suffering from Chronic Glomerulonephritis and IgA Nephropathy followed by Chronic Interstitial Nephritis and obstructive uropathy (1, 14.3%). Out of 57 patients in CKD with Hyperhomocysteinemia group, majority of patients i.e. 43 patients (75.4%) were found in stage 5 CKD, 9 patients (15.8%) in stage 4 and 5 patients (8.8%) in stage 3B. Out of 33 patients in CKD without Hyperhomocysteinemia group, majority of patients i.e. 26 patients (78.8%) were found in stage 5 CKD, 5 patients (15.2%) in stage 4 and 2 patients (6.1%) in stage 3B. Statistical analysis shows there is no significant difference in patients with different CKD stages between CKD with Hyperhomocysteinemia group and CKD without Hyperhomocysteinemia group (p value-0.890). The mean eGFR level was 12.51 ± 9.44 in the CKD with Hyperhomocysteinemia group and 11.67 ± 8.38 in the CKD without Hyperhomocysteinemia group (p=0.672) which was not statistically significant difference in eGFR level between the study groups. The mean Serum Homocysteine level was 20.35±6.47 in the CKD with Hyperhomocysteinemia group and 10.71 ± 2.82 in the CKD without Hyperhomocysteinemia group (p=0.001) which was statistically significant difference in Serum Homocysteine level between the study groups. There is no significant correlation between Hyperhomocysteinemia and occurrence of CKD (p value-0.169) but patients without Hyperhomocysteinemia have less risk of CKD correlation (p value-0.018). Overall there is no significant correlation between Hyperhomocysteinemia and CKD (p value-0.206).

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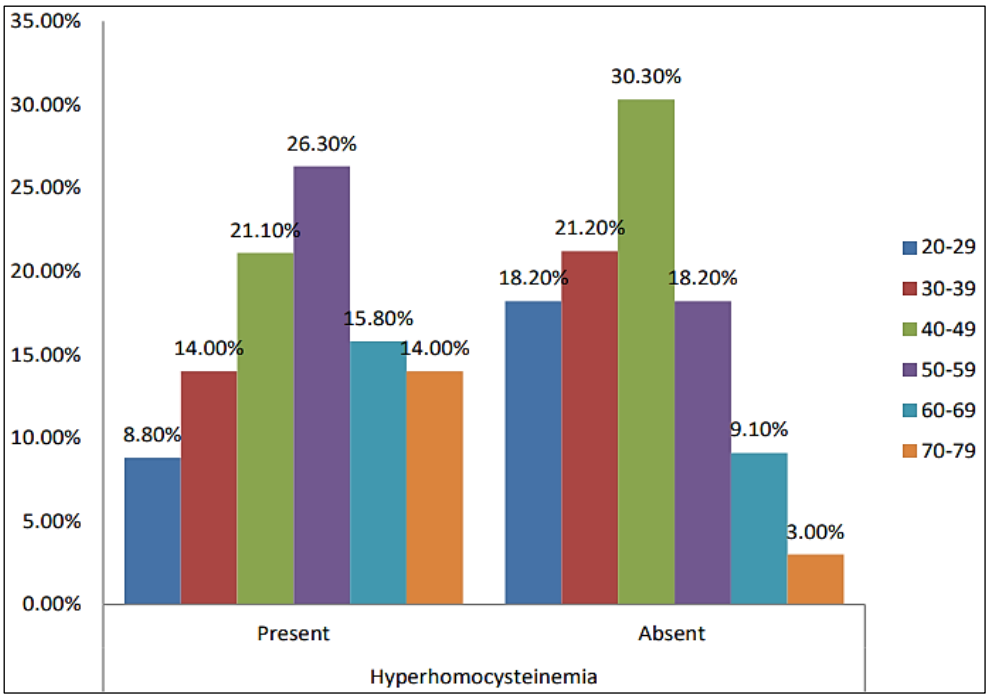

Fig 1: Age distribution among the patients with hyperhomocysteinemia and without hyperhomocysteinemia

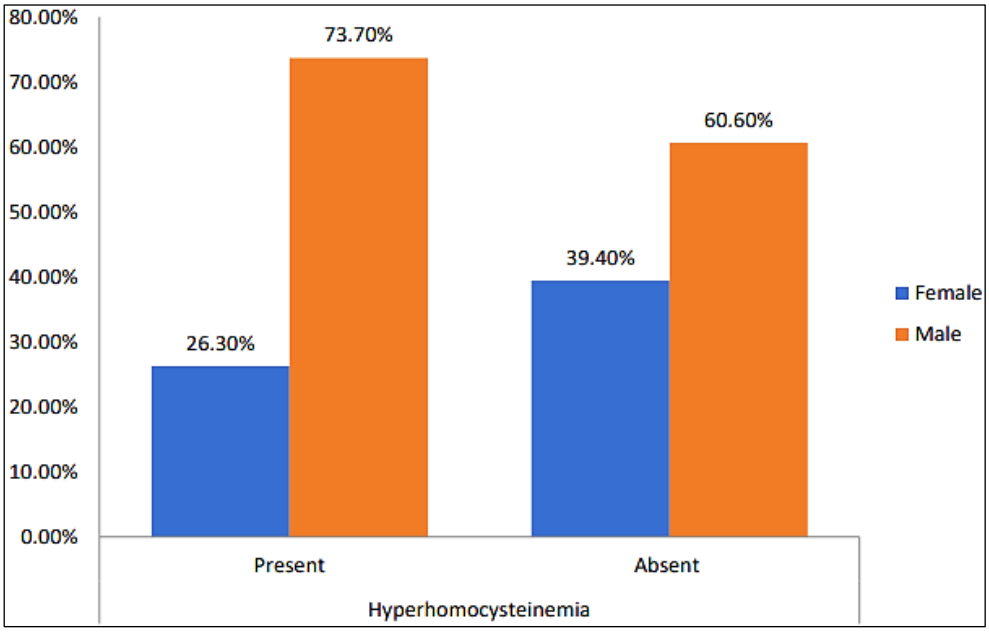

Fig 2: Gender distribution of sample

Table 1: Prevalence of type 2 DM with hyperhomocysteinemia

Diabetes	Hyperhomocysteinemia		Total
	Present	Absent	
Yes	42	13	55
	73.7%	39.4%	61.1%
No	15	20	35
	26.3%	60.6%	38.9%
Total	57	33	90
	100.0%	100.0%	100.0%
p value-0.001			

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Table 2: Correlation of duration of diabetes with hyperhomocysteinemia

Hyperhomocysteinemia	N	Duration of diabetes		Mean difference	p value
		Mean	Std. Dev		
1es	42	9.82	7.073	-0 763	0.458
Nu	13	10.58	8.161		

Table 3: Prevalence of hypertension with hyperhomocysteinemia

Hypertension	Hyperhomocysteinemia		Total
	Present	Absent	
Yes	47	26	73
	82.5%	78.8%	81.1%
No	10	7	17
	17.5%	21.2%	18.9%
Total	57	33	90
	100.0%	100.0%	100.0%
p value - 0.668			

Table 4: Correlation of duration of hypertension with hyperhomocysteinemia

Hyperhomocysteinemia	N	Duration of hypertension		Mean difference	p value
		Mean	Std. Dev		
Yes	4	7.3	6.545	1 434	0.364
No	26	5.87	6.206		

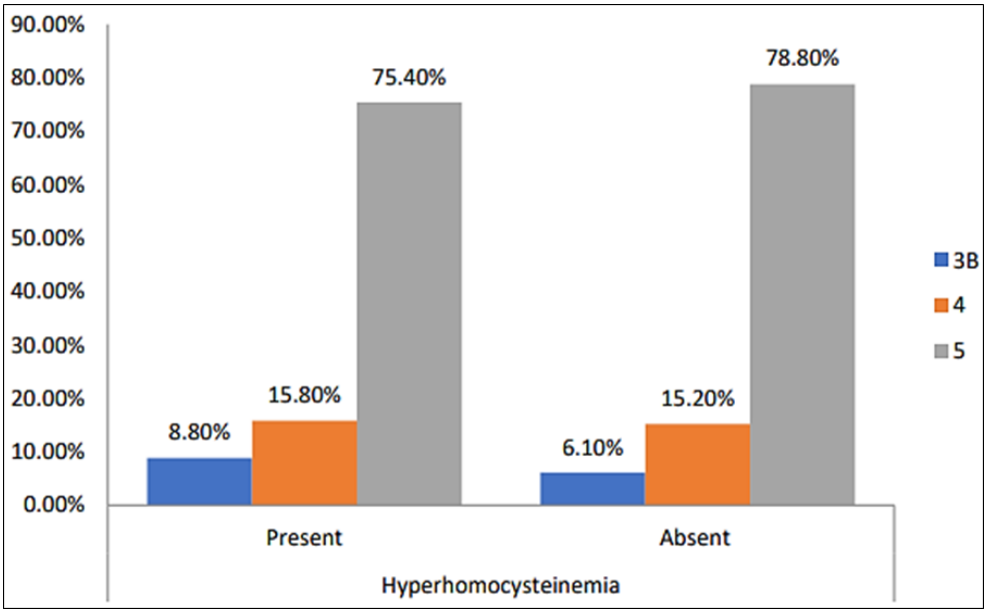

Fig 3: Correlation of CKD stages with hyperhomocysteinemia

Discussion

Recently homocysteine has gained much importance because of its role in vascular thrombosis and genesis of atherosclerosis. Chronic kidney disease is also very much prevalent in the general population, the risk increases substantially in patients with diabetes and hypertension. The patients with CKD are very much susceptible to cardiovascular system involvement related morbidity and mortality. As recent studies have shown an increased prevalence of hyperhomocysteinemia in CKD patients we tried to conduct a study in CKD patients who have underlying diabetes and/or hypertension. The mean age of study population was 50.65 ± 15.01 years in the CKD with Hyperhomocysteinemia group and

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42.85 ± 13.83 years CKD without Hyperhomocysteinemia (p=0.017), suggesting a relation between the increase in life expectancy and the presence of chronic pathologies in the population. Considering that patients were not young, the importance of early CKD and serum Homocysteine screening should be emphasized, since the patients might be affected well before diagnosis. This is in line with the study done by Amos L *et al*. with mean age of 44 ± 8.8 years, a historical prospective study conducted with 3602 participants between 2000 and 2012 resulted that: Annual eGFR decline was 25% higher in subjects with elevated versus normal mean homocysteine level (0.90 ± 0.16 ml/min/1.37 m2 vs. 0.72 ± 0.14 ml/min/1.37 m2, p- 0.001) and elevated mean homocysteine level was highly associated with developing CKD (HR 4.85, 95% CI 2.48–9.49, p b 0.001) [13]. There is male preponderance in our study with 70.7% and 60.6% in CKD with and without Hyperhomocysteinemia group respectively. A study "Prevalence of chronic kidney disease among adults in a rural community in South India: Results from the kidney disease screening (KIDS) project" done by Anupama YJ *et al*. involved around 2091 participants of more than 18 years age the subjects were predominantly young with more than 70% aged below 40 year. There was a female preponderance with females constituting (54.43%) of the population studied [3]. This is because sample size in our study is less and participants of our study were more of those older age group more than 40 years. In our study, around 42 (73.7%) patients had Type 2 Diabetes Mellitus in CKD with Hyperhomocysteinemia and 13 (39.4%) patients had Type 2 Diabetes Mellitus in CKD without Hyperhomocysteinemia. A study "Prevalence of chronic kidney disease in two major Indian cities and projections for associated cardiovascular disease" done by Anand S *et al*. also showed that Chronic kidney disease prevalence among participants with diabetes mellitus was 15.4% (95% CI: 13.5-17.4%), substantially higher than that of participants without diabetes (prevalence difference: 10.5% (95% CI: 8.4-12.6%)). Prevalence was also higher among participants with study diagnosed diabetes mellitus than among participants without diabetes (prevalence difference: 6.9% (95% CI: 4.6-9.2%)) [14]. In present study, around 47 (82.5%) patients had Hypertension in CKD with Hyperhomocysteinemia and 26 (78.8%) patients had Hypertension in CKD without Hyperhomocysteinemia. A study "Prevalence of chronic kidney disease among adults in a rural community in South India: Results from the kidney disease screening (KIDS) project" done by Anupama YJ *et al*. involved around 2091 participants of more than 18 years age the subjects were predominantly young with more than 70% aged below 40 year. Hypertension was seen in 702 (33.62%) subjects of whom only 106 (15.07%) subjects gave a history of hypertension indicating that nearly 84.93%% were unaware of their hypertensive status indicating that Hyperhomocysteinemia is a risk factor for Hypertension and CKD [3]. In our study, majority of patients i.e. 43 patients (75.4%) were found in stage 5 CKD, 9 patients (15.8%) in stage 4 and 5 patients (8.8%) in stage 3B in CKD with Hyperhomocysteinemia group and 26 patients (78.8%) were found in stage 5 CKD, 5 patients (15.2%) in stage 4 and 2 patients (6.1%) in stage 3B in CKD without Hyperhomocysteinemia group. A study done by Zengchun Y *et al*. also presented with the results showing, out of 1042 subjects, the prevalence of Hyperhomocysteinemia in this cohort was 52.78% (550/1042) overall, and 10.73%, 29.22%, 58.71%, 75.23% and 83.75% in CKD stage 1, stage 2, stage 3, stage 4 and stage 5 patients, respectively. Patients with poorer kidney function had a higher prevalence of Hyperhomocysteinemia than patients with better renal function (p-<0.005). The pooled prevalence of Hyperhomocysteinemia significantly increased from 10.73% in CKD stage 1 to 83.75% in CKD stage 5 with the deterioration of renal function. The possibilities may be due to several reasons. Mainly, decreasing kidney function can reduce the renal metabolic extraction of Homocysteine due to the decreasing plasma flow [15]. The present study resulted that elevated serum homocysteine levels appear to be closely associated with CKD and Serum homocysteine levels are negatively associated with eGFR using the Pearson's Correlation analysis. In line with the present study, a cross sectional study "Serum homocysteine level is positively associated with chronic kidney disease in a Taiwan Chinese population" done by Chao M.C *et al*. also concluded that serum homocysteine levels correlate negatively with eGFR and that elevated homocysteine levels are positively associated with

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CKD. The significant increase in odds ratios for CKD with progressively increasing homocysteine levels reveals a dose–response effect [5].

Conclusion

Our study concluded that serum homocysteine levels was significantly elevated in patients with CKD and it correlated well with decline in eGFR as the kidney disease progressed. Diabetes and hypertension were common co-morbidities in CKD patients, therefore, early identification of risk factors that predict cardiovascular morbidity and mortality becomes the need of the hour, especially, in patients with significant co-morbidities like diabetes and hypertension. There are well established biomarkers for determining the progression of kidney disease, serum homocysteine can be considered as a useful marker as it co-relates well with progression of CKD and also considered to be a marker of cardio-vascular disease in CKD. In addition, it needs to be studied whether treatment of hyperhomocysteinemia can prevent progression of CKD.

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