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Original Research Article

PREVALENCE OF CORONARY ARTERY DISEASE IN PATIENTS WITH END STAGE RENAL DISEASE WITH HIGHER CONCENTRATION OF TOTAL HOMOCYSTEINE CONCENTRATION IN BLOOD PLASMA.

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Abstract

The chronic kidney disease stage 3 to 5 (Glomerular filtration Rate GFR 59 to <15), Renal tubular dysfunction and decreased GFR which leads to decreased renal catabolism of homocysteine. Cardiovascular disease (CVD) is a major cause of death both in general population and in End Stage Renal Disease (ESRD), it accounts approx 40%. An analytical cross-sectional study is designed to find out the prevalence of coronary artery disease in patients with hyperhomocysteinemia in end renal disease patients and to discover the correlation between them. The homocysteine concentrations were found 34.66 ± 1.69 µmol/L and 17.6 ± 1.4 µmol/L for the group of patients with and without evidence of Coronary Artery Disease (CAD) respectively. Whereas the mean homocysteine concentrations of the total population were found 24.8 ± 1.85 µmol/L. This showed that patients having higher values of homocysteine concentration in blood plasma have higher chances of having CAD (p<0.050).

Keywords: homocysteine conc., End stage renal disease, coronary artery disease.

Introduction

The term chronic renal failure applies to the process of continuing the significant irreversible reduction in nephron number and typically correspond to the chronic kidney disease stage 3 to 5 (Glomerular filtration Rate GFR 59 to <15)[1]. Renal tubular dysfunction and decreased GFR which leads to decreased renal catabolism of homocysteine and decreased the renal production of serine (80-90%)[2]. Cardiovascular disease (CVD) is a major cause of death both in general population and in End Stage Renal Disease (ESRD), it accounts approx 40% of the total deaths in both demographic group of patients[3]. The risk of CVD is higher in case of patients with ESRD; the mortality in dialysis patients is 10 to 20 times higher[4]. Prominent among the unique renal related risk factors are elevated levels of the putatively atherothrombotic sulfur amino

acid homocysteine. In a pooled observational studies suggest that mild-to-moderate hyperhomocysteinemia (Total Homocysteine levels 12 to 99 µmol/L) is also a significant risk factor for arteriosclerotic CVD among the general population. Patients with chronic renal failure have an excess prevalence of hyperhomocysteinemia[5].

The present study is designed to find out the prevalence of coronary artery disease in patients of end renal disease, to assess the prevalence of hyperhomocysteinemia in end renal disease patients and to discover the correlation between such conditions.

Materials and Method:

The present study was conducted in the post-graduation department of Medicine, S. N. Medical College, Agra. Subjects for the study were selected from the patients admitted to Medicine ward from outdoor and to the emergency ward. A written consent was taken from all the patients selected for analytical cross-sectional study. Inclusion and exclusion criteria were laid down as follows:

Inclusion Criteria

- Patients having End Stage Renal Disease (Chronic Kidney Disease-Stage-5; GFR<15)
- Willingness to take part in the study with informed consent.
- Age between 40 to 70 years

Exclusion Criteria

- Patients having Chronic Kidney Disease stage 1- Stage 4
- Age lesser than 40 years and more than 70 years
- Patients not willing to take part in the study
- Patients with intercurrent infections.

A total of 100 patients having End Stage Renal Disease from indoor, outdoor and the patients from emergency ward were selected for the study. The group of subjects consisted of 52 males and 48 females. All subjects were Indian without any racial preference. The age distribution among the subjects is shown in table 1:

Diagnosis of Coronary Artery Disease (CAD):

CAD was diagnosed as per following criteria[6]

1. Previous admission for documented myocardial infarction (Prolonged chest pain associated with electrocardiogram changes and an elevated creatine kinase level and/or regional wall motion abnormality in 2D Echo)
2. Significant positive result in angiograms (stenosis> 90% for 1 of 3 major vessels or 75% narrowing of the left main coronary artery)
3. Symptoms consistent with angina confirmed to a positive exercise stress test result.

Determination of Total Homocysteine (tHCy) level in blood plasma:[7]

Plasma total homocysteine concentration was determined by fluorescent detection using the method developed by Vester and Rasmussen and further modified by Ubbink et al and J. Genest. Ingestion of food has little effect on homocysteine levels, whereas hemodialysis may decrease level by 30%. Hence predialysis nonfasting level was measured for all the subjects. A blood sample collected was spun into plasma within 30 minutes of blood collection. Samples were stored at -70^{o}C and all assay were conducted in one batch[8].

Predialysis total homocysteine concentration was determined for the whole population and arranged into ascending order accordingly. Then divided into four quartiles each quartile contains 25 subjects.

Determination of Risk factor was for CAD

Risk factor for CAD was defined as per following measurements:

Hypertension (HT): was defined as the requirement for antihypertensive medications or a resting predialysis blood pressure greater than 140 mm Hg systolic and/or 90 mm Hg as diastolic on 3 occasions.

Diabetes Mellitus (DM): was defined as the need of insulin, oral hypoglycemics or diabetic diet or a fasting or random plasma glucose level greater than 7.8 mmol/L or HbA1c> 6.5, respectively/

Family History of CAD: was considered significant if a first-degree relative had premature ischemic heart disease.

Hypercholesteremia: is defined in the patient was receiving lipid-lowering agent or had documented hypercholesteremia (Total Cholesterol > 6.2 mmol/L; LDL > 4.1 mmol/L).

Smoking habit: Active smoker those who currently smoked, ex-smoker who dropped smoking but used to smoke previously and non-smoker who don't have a history of smoking.

Parameter Investigated:

All the following parameters required for the study were investigated as per the standard laboratory procedures:[9]

Serum creatinine, Blood Urea, Electrolytes, ECG, TMT, 2D Echo, Lipid Profile, USG Abdomen, Urine Routine Microscopy, 24 hr urine protein, Coronary angiography.

Statistical Analysis:

The data were analyzed using the software GraphPad Prism (7.03). The results were expressed as Mean ± Standard Deviation (SD). Data were analyzed using unpaired t-test $P<0.05$ was considered as significant. A backward logistic regression was performed using clinically significant CAD as the outcome variable.

Results:

Subject Selection:

Total 100 patients having ESRD aged between 40 to 70 years were selected for the study. Among the selected population 52 were male and 48 were female. The age wise distribution of the total 100 subjects is shown in table 1.

Table 1: Demographic distribution of patients having ESRD on the basis of age and sex; selected for study

Age of the subjects (years)	Male (N= 52)		Female (N=48)		Total (N= 100)	
	No.	%	No.	%	No.	%
40-50	12	23.07%	6	12.5%	18	18%
51-60	26	50%	21	43.75%	47	47%
61-70	14	26.92%	21	43.75%	35	35%
Mean Age	**56.78 ± 8.20**		**60.25 ± 7.51**		**58.57 ± 7.25**	

Baseline characteristics were measured for the assessment of Coronary Artery Disease (CAD) and represented in table 2.

Table 2: Patients with base line clinical complication risk of Coronary Artery Disease

Parameters	Total (N = 100)	Male (N = 52)	Female (N = 48)
Age (years) Mean ± SD	**58.57 ± 7.25**	**56.78 ± 8.20**	**60.25 ± 7.51**
DM	**36 (36%)**	**19 (36.5%)**	**17 (35.9%)**
Hypertension	**87 (87%)**	**44 (82.6%)**	**43 (88.58%)**
Family history of CAD	**23 (23%)**	**11 (21%)**	**12 (25.5%)**
Hypercholestermia	**50 (50%)**	**24 (46.1%)**	**26 (54.1%)**
Ex-Smoker	**19 (19%)**	**8 (15.3%)**	**11 (22.9%)**
Active Smoker	**26 (26%)**	**14 (33.3%)**	**12 (25%)**

Patients having CAD were diagnosed and categorised as shown in Table 3.

Table 3: Percentage of patients assessed for the evidences of CAD

Evidences of CAD	Male (N= 52)		Female (N=48)		Total (N= 100)	
	No.	%	No.	%	No.	%
Evidence of CAD (A)	7	13.4%	4	8.33%	11	11%
Evidence of CAD (B)	5	9.6%	1	2.08%	6	6%
Evidence of CAD (C)	7	13.4%	5	10.41%	12	12%
Total Patients with CAD (A+B+C)	**19**	**36.5%**	**10**	**20.83%**	**29**	**29%**
No Evidences of CAD	**33**	**63.5%**	**38**	**79.17%**	**71**	**71%**

Coronary Artery Disease (A): Previous admission for documented Myocardial Infarction.
Coronary Artery Disease (B): Significant positive Coronary angiography
Coronary Artery Disease (C): Symptoms consistent with angina confirmed by the positive exercise stress test result.

Among the population, 63.5% males and 79.17% females were found with no evidence of Coronary Artery Disease whereas a total of 36.5% of males and 20.83% females were found with different pieces of evidence of Coronary Artery Disease. The results show that risk of Coronary Artery Disease have no sex inclination and there is no significant different ($p<0.05$) between the chances of affecting with CAD for both male and female.

The total homocysteine concentration was determined of the whole population (N=100). The mean total homocysteine concentration was found 24.8 ± 1.85 (µmol/L). Mean total homocysteine concentration of group in patients with evidence of CAD was 34.66 ± 1.69 µmol/L and 17.6 ± 1.4 µmol/L in the group of patients with found with no evidence of CAD depicted in figure 1. All the population was arranged in ascending order and divided into four quartiles. The evidence of CAD and Homocysteine Concentration was reported and represented in table 5.

Figure 1: Total homocysteine concentration (µmol/L) among patients with and without prevalence of CAD

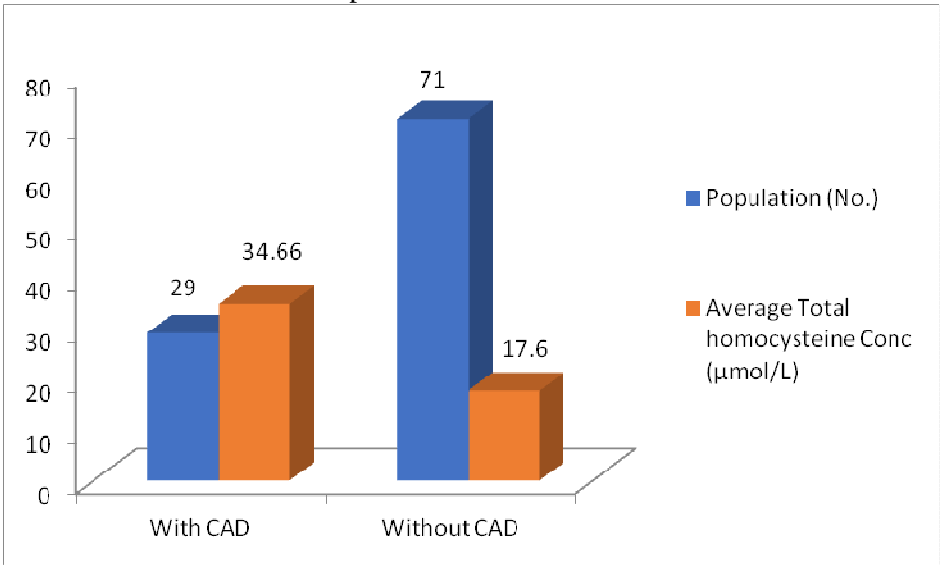
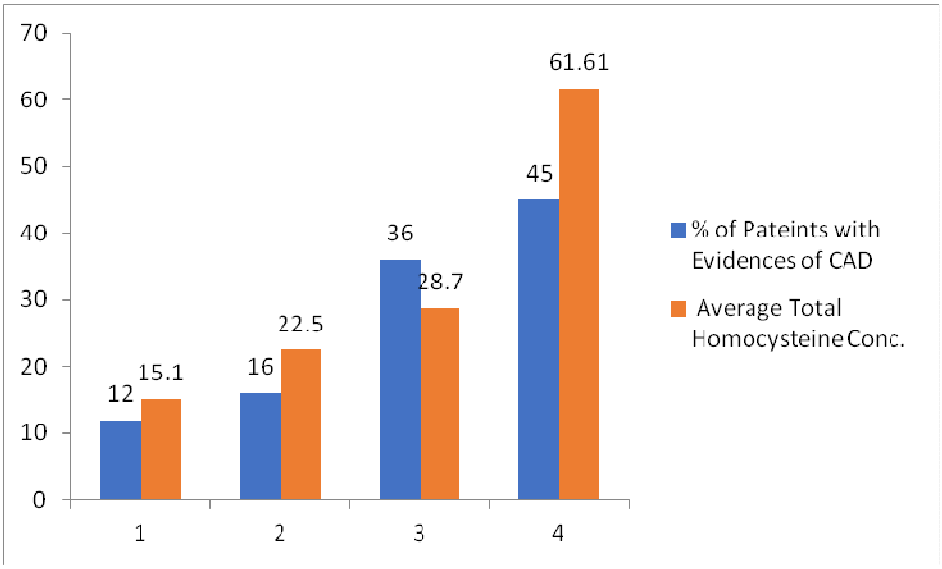


Table 4: Distribution of patients in four quartiles and their clinical measurements

Variables	Quartile 1 (n= 25)	Quartile 2 (n= 25)	Quartile 3 (n= 25)	Quartile 4 (n= 25)
Age (years) (Mean ± SD)	57.88 ± 8.06	58.84 ± 7.22	58.72 ± 3.64	58.84 ± 2.19
Male no. (%)	16 (64%)	10 (40%)	10 (40%)	16 (64%)
Female no. (%)	9 (36%)	15 (60%)	15 (60%)	9 (36%)
Patients with Hypertension	23 (92%)	22 (88%)	22 (88%)	20 (80%)
Pateints with Hypercholesterolemia	15 (60%)	14 (56%)	15 (60%)	16 (64%)
Diabetes Mellitus	9 (36%)	10 (40%)	7 (28%)	10 (40%)
Evidences of CAD (A+B+C)	3 (12%)	4 (16%)	9 (36%)	13 (45%)
Total Homocysteine Conc. (µmol/L) (Mean ± SD)	15.1 ± 1.77	22.5 ± 1.87	28.7 ± 1.55	61.61 ± 1.23
Total Creatinine Level in plasma (Mean ± SD)	8.44 ± 2.97	10.26 ± 3.18	10.91 ± 3.6	10.48 ± 2.19

From the observations, it is evident that in fourth quartile the mean age of subjects was 58.84 ± 2.19 and found significantly ($p<0.05$) high prevalence of CAD of 45% with a high concentration of total homocysteine 61.61 ± 12.3; when compared to other three quartiles depicted in figure 2.

Figure 2: Prevalance of CAD and relative average total homocysteine conc in four quartiles



The unadjusted odds ratio for CAD was 2.4 (95% Confidence interval, 1.27-4.56) when all the five risk factors i.e. Levels of homocysteine, age, sex, DM, and smoking; independently associated with CAD. When adjusted for the effects of age, sex, DM and smoking the odds of CAD as 2.1 fold greater (95% Confidence interval, 1.03 - 4.39) for the patients having higher homocysteine concentration in the fourth quartile when compared to other three quartiles.

Discussion:

From this analytical cross-sectional study, it can be concluded that among the population of 100 patients having End Stage Renal Disease are 29% patients were found with evidence of Coronary Artery Disease and 71% patients were free from any risk of Coronary Artery Disease. The homocysteine concentrations were found 34.66 ± 1.69 µmol/L and 17.6 ± 1.4 µmol/L for the group of patients with and without evidence of CAD respectively[10]. Whereas the mean homocysteine concentrations of the total population were found 24.8 ± 1.85 µmol/L. This showed that patients having higher values of Homocysteine concentration in blood plasma have higher chances of having CAD ($p<0.050$). This is also supported by the higher level of concentration of homocysteine in fourth quartile i.e. 61.61 ± 1.23 µmol/L, have significantly higher ($p<0.05$) evidence of 45% of CAD[11]. Backward Logistic Regression also shows the independent correlation of CAD with homocysteine levels (95% confidence interval).

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