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Cardiovascular risk factors in chronic kidney disease stage-V: A tertiary centre experience

Medical Science

KEYWORDS : Chronic Kidney Disease, Cardiovascular Risk Factors, Estimated glomerular filteration rate.

Dr. Munna Lal Patel	MD, Assistant Professor, Department of Medicine (Nephrology Unit), King George's Medical University, Lucknow, UP, India
Prof. Rekha Sachan	MS, FICOG, Professor, Department of Obstetrics & Gynaecology,, King George Medical University, (U. P.) Lucknow
Dr. Radheshyam	Assistant professor, Department of Geriatric ICU, King George Medical University, Lucknow
Dr. Pushpalata Sachan	Lecturer, Department of Physiology, Career Institute of Medical Sciences, Lucknow

ABSTRACT

Background: CKD is defined by the presence of kidney damage or decrease function irrespective of cause for three or more months. The term kidney failure is the end stage of CKD with severe reduced function or dialysis. CVD is the leading cause of morbidity and mortality in CKD patients, accounting for 40% of hospitalization and almost 50% of deaths. This Prospective cross sectional study was carried out over a period of one year.

The aim of this study was to observe CKD specific cardiovascular risk factors and cardiovascular events among patients with CKD stage –V before initiation of dialysis.

Methods: 290 CKD stage-V patients were evaluated as per inclusion criteria (age more than 18 years and patients with CKD stage-V (Estimated glomerular filtration rate (eGFR) <15ml/min/1.73m2 for more than three months). 5 ml of venous blood sample was collected after overnight fasting. The level of serum urea, creatinine, albumin, cholesterol, triglyceride, high density lipoprotein (HDL), low density lipoprotein (LDL), phosphorus, calcium, hemoglobin, glucose were measured. Spot urine samples were tested for albumin/creatinine ratio (ACR). Estimated glomerular filteration rate was estimated using Modification of Diet in Renal Disease

Results: Among traditional risk factors 87.9% had hypertension, and 22.4% had diabetes mellitus. Regarding dyslipidemia 44.6% had raised LDL cholesterol and 57.3% had showed increased triglyceride level. Anemia showed the highest prevalence (94.2%) among CKD specific factors. More than 50% of study population had hypocalcemia and hyperphosphoatemia. Prevalence of cardiovascular events in CKD-V patient showed that 20.5% had ischemic heart disease, 40% heart failure, 5.2% arrhythmias and 20% had left ventricular hypertrophy. More than half of patient had cardiovascular events about one third had single events and rest of the patient have two or more cardiac events.

Conclusion: The result of this study suggests that both cardiovascular risk factors and events are prevalent among patients with CKD stage-V.

Introduction

Chronic kidney disease is now being recognized as major public health problem that is threatening to reach epidemic proportions ever the next decade.1 The annual incidence of end stage renal disease (ESRD) in USA, UK and Europe is 33.6, 10, 13.5 per one lac population respectively.[2] The incidence of chronic kidney disease has not been studied well in India. The CKD registry has published its data and reported an analysis from all over India and found diabetic nephropathy 31%, CKD of undetermined etiology 16%, chronic glomerular nephritis 14% and hypertensive nephropathy 13%.[3]

CKD is defined by the presence of kidney damage or decrease function irrespective of cause for three or more months. The term kidney failure is the end stage of CKD with severe reduced function or dialysis. End stage renal disease (ESRD) are chronic renal failure treated with dialysis or transplantation. The KDIGO have classified CKD based on glomerular filteration rate (GFR), albuminuria, dialysis dependent or not and etiology of CKD.[4]

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in CKD patients, accounting for 40% of hospitalization and almost 50% of deaths. The risk of death from CVD is elevated 30 fold for patient with ESRD as compared to the general population. At the time of starting renal replacement therapy, prevalence of cardiovascular disease among CKD patient is high,[5,6] Many of the CKD-V patients can not start or unfit to continue dialysis because of cardiovascular diseases. Cardiovascular events are the leading causes of mortality among dialysis patients. It has been widely shown that the cardiovascular status at the beginning of dialysis greatly affects patients outcome.[6] There is accumulating evidence that the increase in CVD burden is present in patients prior to dialysis, due to both conventional risk factors as well as those specific to kidney disease.[7]

Risk factors for the increased prevalence of CVD in CKD include Traditional risk factors like age, sex, diabetes, hypertension, smoking, obesity, and those specific to CKD, blood pressure changes, fluid, imbalance, anemia, calcium/phosphorus metabolism, malnutrition, hypoalbuminuria. Hyperhomocystenemia, inflammation, oxidative stress, insulin resistance, altered rennin-angiotensin axis and endothelial dysfunction .[8]

There is very few studies related to CKD specific cardiovascular risk factors among non dialytic patients with CKD stage-V. Base line information about cardiovascular risk factors before starting dialysis among CKD stage-V patients is essential to develop effective preventive and control strategy for the prevention of cardiovascular events in CKD patients. The aim of this study was to observe CKD specific cardiovascular risk factors and cardiovascular events among patients with CKD stage-V before initiation of dialysis.

Material and Methods:

This study was conducted in department of Medicine, King George's Medical University, Lucknow for a period of one year from 2012 to 2013 after written informed consent and ethical clearance from the institutional ethics committee. 310 CKD stage-V patients were enrolled in the study as per inclusion criteria (age more than 18 years and patients with CKD stage-V ` (Estimated glomerular filtration rate (eGFR) <15ml/min/1.73m^2 for more than three months). 20 patient were dropped out. Patients age less than 18 years and CKD stage-V on hemodialysis were excluded from the study.

5 ml of venous blood sample was collected from patients who agreed to participate in the study after overnight (12-14 hours) fasting. The level of serum urea, creatinine, albumin, cholesterol, triglyceride, high density lipoprotein (HDL), low density lipoprotein (LDL), phosphorus, calcium, hemoglobin, glucose were measured. Spot urine samples were tested for albumin/creatinine ratio (ACR). The ACR was calculated as ACR(mg/

gm= microalbumin in urine (mg/l) X1000 / creatinine in urine (mg/dl) X10. Estimated glomerular filteration rate (eGFR) was estimated from serum creatinine level by using Modification of Diet in Renal Disease (MDRD), prediction equation (eGFR) ml/min/1.73m2=186X (S. Creat.)-1.154 X(Age)-0.203 X(0.742 if female). Height, weight and blood pressure were measured for each patients. Height was measured to the nearest 1.0 cm and weight to the nearest 0.1 kgs. BMI was calculated by dividing the weight in kilograms by the square of the height in meters. Blood pressure was measured in right arm, with the subject in a relaxed, sitting position. The average of two measurements with a mercury sphygmomanometer was used for all subjects.

CKD specific cardiovascular risk factors were, anemia, C-reactive protein serum Ca++, serum PO4- - -and Ca X PO4- - -product. Traditional cardiovascular risk factors were hypertension, diabetes mellitus, age, sex, obesity, smoking and dyslipidemia and cardiovascular events were ischemic heart disease (IHD), congestive heart failure, (CCF). We included clinical ECG and radiological criteria to define cardiac events. Anemia was defined as when hemoglobin <11gm/dl in premenopausal women and when <12 gm/dl in men and post menopausal women.9 To define ischemic heart disease we had included known case of ischemic heart disease or new cases of ischemic heart disease.10 Arrythymia was defined as atrial or ventricular rhytham disorder requiring therapy.10 Cardiac failure was defined as persistant or recurrent dyspnoea plus two of the following raised jugular venous pressure, bibasilar crackles, pulmonary venous hypertension, or interstitial edema on chest X-ray. 11 Left ventricular hypertrophy was defined by ECG as R-wave amplitude ≥25mm defletion in any precordial leads, R-wave amplitude ≥20mm in standard leads, R-wave amplitude ≥11mm in augmented unipolar leads, R-wave amplitude in V5 or V6 plus S-wave amplitude in V1 or V2 ≥35mm. ST segment characteristic depressed S-T segment, flattened to inverted T wave. 12,13

Complete hemogram will be done by automated cell counter (Melet Schloesing laboratories France), Blood urea (UV Kinetic), serum creatinine (Jaffee's method), eGFR (MDRD Equation), serum calcium (Arcenazo Method), serum phosphorous (UV end point), serum uric acid (Uricase method), C-reactive protein (Nephalometry methods), USG abdomen, lipid profile (estimation of total cholesterol by cholesterol oxidase/phenol aminoantipyrine method, estimation of HDL cholesterol by cholesterol oxidase/phenol aminoantipyrine method, estimation of LDL cholesterol by Friedewald formula (cholesterol - HDL + Triglyceride/5), estimation of triglycerides by glycerol phosphate oxidase-phenol aminoantipyrine method).

Statistical Analysis:
Data entry and statistical analysis were performed using SPSS (Statistical package for social sciences) software package version 11. The variables were analyzed using descriptive statistics and independent samples t-test. Results were expressed as frequency or mean ±SD. The association between two or more categorical variables was tested by $\chi 2$ statistics by using appropriate correction. The results were statistically significant when the p value was less than 0.05.

Observation and Results:
Among study population mean age of the patients was 45.3±14.5 years, the lowest and highest ages were 18 and 70 years respec¬tively. 25.1% was below 30 years of age, 20.1% between 30-40 years, 17.4% between 40-50 years, 16.7%, between 50-60 years and 17.1% subjects were between 60 to 70 years. 62% of the patients were male and the rest 38% were female giving a male to female ratio of roughly 2:1. About 68% of patients were rural resident and rest 32% were urban residents. Etiology of CKD was glomerulonephritis (42.1%), diabetes (34.8%), hyperten¬sion (20%) and 3.1% were suffering from other causes.. (Table I)

Among traditional risk factors 87.9% had hypertension, and 22.4% had diabetes mellitus. Regarding dyslipidemia 44.6% had raised LDL cholesterol and 57.3% had showed increased triglyceride level, 29.3% had habit of smoking where as 20.6% was suffering from obesity. (Table I)

Anemia showed the highest prevalence (94.2%) among CKD specific factors. More than 50% of study population had hypocalcemia and hyperphosphoatemia. CaXP products was elevated in among 24.1% of population. More than 80% of CKD patients were positive for C-reactive protein an acute phase protein. (Table II)

Body mass index and smoking habits almost were identically distributed between two groups (p=0.565 and p=0.887 respectively). The prevalence of anemia and hypertension had no significant difference (p=0.186 and p=0.537) respectively between groups. Diabetes was significantly higher in patients with cardiovascular complication than those without cardiovascular complications (p=0.025) (Table III & IV)

Female with CKD were significantly prone to develop cardiovascular events like ischemic heart disease, heart failure arrhythmia left ventricular hypertrophy than their male counterpart (p=0.047). But age was not found to have significant association with cardiovascular events (p=0.081). None of these CKD specific factors had any significant difference between subjects who develops cardiovascular events and subjects who did not developed cardiovascular events (p=>0.05 in each case) (Table III)

Prevalence of cardiovascular events and CKD Stage - V patient showed that 20.5% had ischemic heart disease, 40% heart failure, 5.2% arrhythmias and 20% had left ventricular hypertrophy. More than half of patient had cardiovascular events about one third had single events and rest of the patient have two or more cardiac events. (Table V)

Discussion
There are several cardiovascular risk factors which are specific for CKD. Anemia, hypocalcemia, hyperphosphatemia, calcium phosphate product, inflammatory proteins, like C-reactive protein and homocystinemia are specific factors responsible for cardiovascular disease in CKD patients. Anemia which is thought to make a substantial contribution to the development of cardiac abnormalities in CKD patients, is a very frequent complication. Anemia is itself responsible for left ventricular hypertrophy which is the hallmark of cardiovascular events. A number of observational studies have shown that it inversely correlates with residual renal function, yet its prevalence is already high during the earlier stages of CKD.14-16

In a large scale study of hemodialysis patients, higher hyperphosphataemia levels were significantly associated with an increased risk of death, even after adjusting preexisting medical condition, the delivered dialysis dose, estimates of nutritional status and estimates of non-compliance.17 These results, which have been confirmed by another study.18 Other study also demonstrate that hyperphosphataemia directly contributes to the excessive mortality of CKD patients, in which it recently has been defined as a "silent killer".19 The exact mechanisms by which hyperphosphataemia leads to increased mortality have not yet been completely clarified but they probably involve the calcification (due to increased calcium phosphate product or secondary hyperparathyroidism) of coronary plaques, cardiac valves and myocardial tissue.20 According to our study anemia was found to be most prevalent (95%) among CKD specific risk factors. Hypocalcemia (56.8%) and hyperphosphatemia (60%) also showed higher distribution in study population CaXP product was elevated among (24%) of population.

Hypertension diabetes mellitus, smoking dyslipidemia and old age are established risk factors for development of cardiovascular disease in CKD patients. In a study it was found that age, gender smoking, previous cardiovascular disease, hypertension, diabetes and total serum cholesterol were all significantly increased (p<0.001) in patients with estimated creatinine clearance of <60 ml/min.21 In our study among traditional risk factors more than 50% had hypertension, high LDL cholesterol and high triglycerides where as prevalence of diabetes, smoking habit and obesity was less than 30%. As a whole all the major

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risk factors that we had seen in our study, were present in significant number among study population.

It is established that high serum concentrations of markers of systemic inflammation including C-reactive protein and interleukin-6 have been associated with atherosclerosis22,23 and increased cardiovascular mortality in CKD patients.24-26 In our study 82% of CKD-V patients were positive for C-reactive protein this high inflammatory protein clearly indicates that most of CKD-V patients are in great risk of developing atherosclerosis and cardiovascular diseases.

Prevalence of cardiovascular events in CKD-V patient showed that 20.5% had ischemic heart disease, 40% heart failure, 5.2% arrhythmias and 20% had left ventricular hypertrophy. More than half of patient had cardiovascular events about one third had single events and rest of the patient have two or more cardiac events. A large scale study from western countries revealed that clinical manifestation of cardiovascular disease were highly prevalent at the start of ESRD treatment. 14% had coronary artery disease, 19% angina pectoris, 31% cardiac failure, 07% dysarrhythmia and 8% peripheral vascular disease. In echocardiography 15% had systolic dysfunction, 32% left ventricular dialatation and 74% left ventricular hypertrophy. The overall median survival time was 50 months.27

Although LVH is very frequent among CKD patients, in our study prevalence of left ventricular hypertrophy was underestimated (20%) because only ECG criteria was used for detection of LVH. The Canadian Multicentre Study of Renal Anemia in patients with various stages of CKD found that the prevalence of LVH progressively increased with delivering renal function from the 30% prevalence at an early CKD stages.28

Our study result showed that age had no significant association with cardiovascular event (p=>0.05). Diabetes was significantly higher in patients with cardiovascular complications than that in patients without cardiovascular complication (p=0.025) Female were significantly prone to develop cardiovascular events than their male counterpart (p=<0.05). But it was seen that anemia, hypertension, smoking and obesity had no significant relationship to develop cardiovascular events (p=>0.05). In addition none of the CKD specific risk factors were significantly associated with cardiovascular complication.

The prevalence of both cardiovascular risk factors and events was high in our study but it was failed to find out significant association between most of the cardiovascular risk factors and cardiovascular events among CKD stage-V patients before starting dialysis therapy because most of our study population was below fifty years and major cause of CKD in our study population was glomerulonephritis. Further a large scale study of different age group and various etiology of CKD required to explore the exact prevalence of cardiovascular risk factor in CKD patients.

Conclusion

Cardiovascular diseases are the leading causes of morbidity and mortality among CKD patients. The result of this study suggests that both cardiovascular risk factors and events are prevalent among patients with CKD stage-V. Female sex and diabetes mellitus are significantly associated with cardiovascular events in same group of patients. A large scale study is essential for detection and management of CKD specific cardiovascular risk factors in the early stages of CKD to prevent and halt the morbidity and mortality in CKD patients.

Table 1. Demographic Profile.

Age		
<30 yrs	75	25.1%
30-40 yrs	60	20.1%
40-50 yrs	52	17.4%
50-60 yrs	50	16.7%
60-70yrs	51	17.1%
Gender Male	180	62%
Gender Female	110	38%
Rural	197	68%
Urban	93	32%
Etiology of CKD		
Glomerulonephlro	122	42.1%
Diabetes	101	34.8%
Hypertension	58	20%
Other causes	9	3.1%
Traditional Risk Factors		
Diabetes mellitus	65	22.4%
Hypertension	255	87.9%
Anemia	273	94.2%
Smoker	85	29.3%
Increased LDL	134	44.6%
Increased Triglyceride	172	57.3%
Obesity	60	20.6%

Table 2. Distribution of patients by CKD specific Risk factor (n=290)

Specific factor related to CKD	Frequency	Percentage
Anemia	273	94.2%
Hypocalcemia (<8.1mg/dl)	165	56.9%
Hyperphosphatemia (>5.5mg/dl)	174	60%
Product of calcium and phosphate ($>55mg^2/dl^2$)	70	24.13%
C-Reactive Protein	240	82.75%

Table 3. Association between Traditional risk factors and CV events. (n=290)

Traditional risk factor	Cardiovascular events		p value
	Present (n=140)	Absent (n=150)	
Smoking habit			
Smoker	45 (32.14%)	40(26.7%)	0.887
Nonsmoker	95(67.86%)	110(73.3%)	
BMI (nutritional status)			
Underweight & normal	120 (85.71%)	125 (83.3%)	0.565
Overweight and obese	20(14.29%)	25(16.7%)	
Anemia (<12gm/dl)			
Present	138(98.57%)	135 (90%)	0.186
Absent	02(1.43%)	15(10%)	
Hypertension			
Present	125(89.3%)	130(86.7%)	0.537
Absent	15(10.7%)	20(13.3%)	
Diabetes mellitus			
Present	40(28.57%)	25(16.7%)	0.025
Absent	100(71.43%)	125(83.3%)	

Table 4. Association between CKD specific factors and cardiovascular events (n=290)

Specific factors related to CKD	Cardiovascular events		p value
	Present (n=140)	Absent (n=150)	
Raised LDL (>100mg/dl)	64(45.7%)	70(46.7%)	0.413
TG (>150mg/dl)	90(64.3%)	82(54.7%)	0.485
Low HDL(<40mg/dl)	115(82.2%)	125(83.4%)	0.103
Hypocalcemia (<8.1mg/dl)	80(57.15%)	88(58.7%)	0.246
Hyperphosphatemia (>5.5mg/dl)	75(53.58)	88(58.7%)	0.298
Product of calcium and phosphate ($>55mg^2/dl^2$)	32(22.86%)	35(23.4%)	0.892
C-reactive protein (positive)	115(82.14%)	110(73.4%)	0.346

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