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# TO STUDY THE CARDIOVASCULAR RISK FACTORS IN PATIENTS OF CHRONIC RENAL FAILURE IN CENTRAL INDIA

Nephrology

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## ABSTRACT

**Aims and Objectives:** To study cardiovascular risk factors in patients of chronic kidney disease (CKD) and correlation with various clinical, radiological and biochemical parameters.

**Material and Methods:** A total number of 60 patients with CKD aged 21-60 years were recruited from the Department of Nephrology who fulfilled the inclusion criterion, after taking informed consent.

**Results:** Increased levels of serum creatinine and blood urea were associated with increased severity of disease. Severity of anemia was related to the duration and extent of CKD. Low serum calcium levels and high phosphate levels were associated with adverse outcome. Lipoprotein (A) and carotid artery intimal thickness showed positive relation with progression of CKD.

**Conclusion:** ESRD patients are associated with deranged metabolic parameters which leads to increased cardiovascular risk. The increase in cardiovascular risk among patients of CKD is secondary to accumulation of risk factors.

## KEYWORDS

Cardiovascular, Chronic Renal Failure, Risk Factors

## INTRODUCTION

Chronic kidney disease (CKD) encompassed a spectrum of different pathologic process associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR).[1] CKD is emerging as a major public health problem globally. The increase in number of patients can be partially attributed to the epidemic of chronic diseases and aging population.

Recognizing CKD as a major health issue of growing importance, the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) developed standardized terminology for the definition of CKD and its classification based on disease severity, determined by using estimated GFR. NKF-K/DOQI criterion for the definition of chronic kidney disease include: (1) kidney damage for 3 months or longer, defined by structural or functional abnormalities of the kidney with or without decreased GFR, manifested by either pathological abnormalities or markers of kidney damage, including abnormalities in blood and/or urine composition or abnormalities in imaging test results; or (2) GFR less than 60 ml /min per 1.73m$^2$ for 3 months or longer, with or without kidney damage.[1,2]

The 2 major outcomes of patients of CKD stages 1 to 4 are progression of kidney disease, including development of kidney failure and development of cardiovascular disease. Patients on dialysis have high risk of left ventricular hypertrophy, congestive heart failure and ischemic heart disease suggesting that the excess risk of CVD begins in the early stages of chronic kidney disease. It is well recognised that patients with heart failure have decreased kidney perfusion that, at times, may lead to kidney failure, and patients with coronary disease have a greater prevalence of reno-vascular disease, which in turn may promote the progression of kidney disease.[3]

Two main types of risk factors namely traditional and nontraditional come into play in patients with CKD. Traditional risk factors include: age, male sex, hypertension, higher cholesterol, lower HDL cholesterol, DM, smoking, physical activity menopause, family history of CVD and LVH. Non-traditional risk factors include albuminuria, hyperhomocysteinemia, anemia, abnormal calcium phosphate metabolism, fluid overload, oxidative stress, inflammation malnutirion, thrombogenic factors abnormal vascular calcification and altered nitric oxide/endothelin balance. Recently serum lipoprotein-A has been also associated CVD in patients of CKD. With this background, the present study was carried out to study cardiovascular risk factors in patients of chronic renal failure and study its correlation with various clinical, radiological and biochemical parameters.

## MATERIAL AND METHODS

A total number of 60 patients aged 21-60 years were recruited from the Department of Nephrology who fulfilled the inclusion criterion, after taking informed consent.

Inclusion criteria included patients in stage 1 to 5 of chronic kidney disease (CKD). The diagnosis of CKD was made on the basis of NKF/DOQI guidelines.

Patients excluded from the study were less than 20 years and greater than 60 years of age. Patients with cardiovascular disease like atrial fibrillation, valvular heart disease, prosthetic heart valves, infective endocarditis and cardiomyopathy, patients with predisposing factors to dyslipidemia like liver disease and hypothyroidism, patients on drugs that may alter lipid levels like statins, alpha and beta blockers, patients with evidence of inflammatory disease, autoimmune disorders, neoplasms and disseminated intravascular coagulation and patients diagnosed to have genetic lipid disorders.

The patients were classified into various stages of CKD (stages 1-5) as per NKF/DOQI classification. The patients were divided into three groups:

Group I (n=20): subjects with CKD (stage 1 and 2) on conservative therapy for 3 months.

Group II (n=20): subjects with CKD (stage 3 and 4) on conservative therapy for 3 months.

Group III (n=20): subjects with CKD (stage 5) on regular hemodialysis for at least 3 or 4 weeks.

The patients in all the groups were followed for six months and all the relevant investigations were carried out, initially at the time of presentation, and then at 3$^{rd}$ and 6$^{th}$ months interval. A detailed history was taken and a thorough physical examination was performed. Various anthropometrical parameters like height and weight were measured in all patients. Body mass index was calculated from standard nomograms. The investigations carried out were: complete haemogram, blood urea, blood sugar, serum sodium, potassium, serum creatinine, serum uric acid, serum calcium, phosphate, serum protein with A:G ratio and creatinine clearance. ECG, x-ray chest (PA view), serum lipid profile, serum lipoprotein (A) levels and bilateral carotid artery doppler study was also done. In some cases serum lipoprotein (a) levels and carotid ultrasound study was also carried out.

Lp(A) levels was estimated by immunoturbidimetric method for quantifying Lp(A) in serum base on latex enhanced particle agglutination technology. Carboxylated latex particles 9diameter 240 mm) covalently, coated with F (ab')2 fragments of anti-lipoprotein (a) antibodies were incubated with the sample for 5 min at 37 degrees C, and the resulting agglutination was quantified by measuring the change of turbidity produced at 700 nm on the analyser. The assay range was around 0.03-0.9g/l. The significant value will be taken above 30mg/dl.

Carotid sonography was done by a broad band linear array Transducer (7.5-13.0 Mhz frequency). The carotid arteries were examined bilaterally up to the bifurcation and including proximal part, of Internal carotid artery (ICA) and external carotid artery (ECA). The intimal – medial thickness (normal value -0.90 mm), plaque characterisation including echo texture, calcification and cavitations were assessed, initially by gray scale ultrasound and further color flow imaging and conventional duplex scanning was done.

## RESULTS

It was a prospective study for six months. During the study, five patients died and 8 patients deteriorated, out of which three patients lost follow up after 3 months.

**Table 1 Demographic variables / basal renal function investigations**

| Parameters | Group I | Group II | Group III |
|---|---|---|---|
| Mean age | 36.1±11.78 | 40.8±11.81 | 44.8±11.74 |
| Sex ratio (M:F) | 7:3 | 9:1 | 13:7 |
| BMI | 21.7±3.8 | 20.1±3.6 | 20.9±3.1 |
| GFR (ml/min) | 79.5±15.7 | 30.5±12.6 | 8.8±6.2 |
| Hemoglobin (gm%) | 10.9±2.1 | 8.6±1.9 | 6.8±2.5 |
| Blood urea (mg%) | 106.5±70.8 | 160.5±15.7 | 221.3±50.5 |
| Serum creatinine (mg%) | 1.7±0.8 | 3.6±1.5 | 5.7±2.5 |
| Serum uric acid (mg%) | 7.0±2.3 | 8.4±2.4 | 8.9±2.6 |
| Serum calcium (mg%) | 9.2±8.4 | 8.0±0.84 | 7.8±1.1 |
| Serum pholsphate (mg%) | 4.6±1.3 | 6.4±2.3 | 7.5±1.4 |
| Serum lipoprotein – A (mg/dl) | 14.7±8.74 | 49.2±20.2 | 76.7±18.2 |
| Serum potassium (mEq/l) | 4.34±4.4 | 4.4±0.88 | 5.1±0.83 |

The above table shows various demographic parameters and basal renal function investigations observed in the study. In our study, enrolled patients were divided according to etiology of CKD and we found diabetic nephropathy in 31% patients, hypertensive nephropathy in 28%, obstructive uropathy in 13%, chronic glomerulonephritis in 10%, adult polycystic kidney disease in 9% and nehrotic syndrome in 9%.

**Table 2 Renal function tests at various time intervals**

| Group I | Clinical findings | Basal | At 3 months | At 6 months |
|---|---|---|---|---|
| I | Blood urea | 106.5±70.8 | 67.3±35.8 | 50.4±19.2 |
| II | (mg%) | 160.5±65.6 | 142±48.1 | 102.6±42.4 |
| III | | 221.3±50.5 | 206.6±48.2 | 165.6±28.4 |
| I | Serum creatinine | 1.7±0.8 | 1.6±1.0 | 1.2±0.4 |
| II | (mg%) | 3.6±1.5 | 3.4±1.0 | 2.8±1.0 |
| III | | 5.7±2.5 | 5.6±2.0 | 4.4±1.3 |
| I | Serum uric acid | 7.0±2.3 | 5.8±1.1 | 5.2±1.0 |
| II | (mg%) | 8.4±2.4 | 7.5±2.1 | 6.6±1.9 |
| III | | 8.9±2.6 | 8.5±1.9 | 6.9±1.4 |
| I | Hemoglobin | 109±2.1 | 11.03±1.81 | 12.3±1.7 |
| II | (gm%) | 8.6±1.9 | 9.4±1.6 | 9.9±2.0 |
| III | | 6.8±1.54 | 8.1±1.4 | 9.3±1.4 |
| I | Serum calcium | 9.2±0.84 | 9.2±0.72 | 9.6±0.41 |
| II | (mg%) | 8.0±0.84 | 8.8±0.65 | 9.1±0.68 |
| III | | 7.8±1.1 | 8.2±0.71 | 9.0±0.69 |
| I | Serum phosphate | 4.6±1.3 | 4.3±1.0 | 3.7±0.7 |
| II | (mg%) | 6.4±2.3 | 5.6±1.3 | 4.4±1.1 |
| III | | 7.5±1.4 | 6.8±1.2 | 5.9±2.8 |
| I | Serum | 14.1±8.7 | 13.7±7.8 | 13.2±8.2 |
| II | liporotein(a) | 49.2±20.2 | 48.7±19.0 | 47.3±19.0 |
| III | (mg/dl) | 76.7±18.2 | 75.8±17.7 | 74.5±16.9 |

Above table shows various renal function tests carried out in the enrolled patients. As shown in table, in patients in the group III, who were mostly on regular hemodialysis, the blood urea remained persistently high throughout the study. Serum creatinine levels were persistently high in group III indicating the increasing severity of disease. Serum uric acid levels were raised in group II and III. Anemia was present in all the groups, more so in group II and III. Group III patients had severe anemia, when compared to other groups. Thus, the severity of anemia was related to the duration and extent of kidney failure. Serum calcium levels were significantly less in group II and group III as compared to group I. Similarly, basal values of serum phosphate in group I was 4.6±1.3, in group II it was 6.4±2.3 in group III it was 7.5±1.4. The levels were significantly more in group III followed by group II and I. Patients in group III had 5 to 10 times higher levels of lipoprotein A compared to patients in group I.

**Table 3 Intima media thickness of carotid artery at baseline (mm)**

| Group | Common carotid artery | | Internal carotid artery | | External carotid artery | |
|---|---|---|---|---|---|---|
| | Left | Right | Left | Right | Left | Right |
| I | 0.5±0.08 | 0.52±0.11 | 0.49±0.11 | 0.52±0.12 | 0.53±0.09 | 0.5±0.13 |
| II | 0.7±0.10 | 0.68±0.012 | 0.6±0.07 | 0.69±0.08 | 0.62±0.06 | 0.61±0.06 |
| III | 0.8±0.16 | 0.74±0.15 | 0.65±0.08 | 0.74±0.06 | 0.67±0.10 | 0.64±0.09 |

The CA-IMT in the left common carotid artery increased in group II and III as compared to group I and was highly significant ($p < 0.001$).

**Table 4 Plaques and stenosis seen in carotid arteries**

| Group | Total no. of patients having plaques and stenosis | Percentage (%) having plaques and stenosis |
|---|---|---|
| I | 0 | 0% |
| II | 4 | 20% |
| III | 10 | 50% |

The maximum number of patients having plaques and stenosis were seen in group III (50%), followed by group II (20%). No plaques were seen in patients of group I, indicating that presence of plaques and stenosis in carotid arteries increased with the severity of chronic kidney disease.

## DISCUSSION

Patients on dialysis have high risk of left ventricular hypertrophy, congestive heart failure and ischaemic heart disease suggesting that the excess risk of CVD begins in the early stages of chronic kidney disease. Patients with CKD also experience a high rate of fatal and nonfatal CVD events before reaching kidney failure. Patients in all stages of CKD therefore are considered in the "high risk group" for development of CVD and recent guidelines and position statements have defined CKD as a CVD risk equivalent.[1,2]

Herzog et al examined outcomes of 34,189 long term dialysis patients from the US renal data system who were hospitalised between 1977 and 1995 with acute myocardial infarction.[3] Cardiac disease was the single most important cause of death in long term dialysis, accounting for 44% of overall mortality, the recent renal data system report also reported the incidence of hypertension and coronary artery disease was higher in patients of CKD. [4]

Patients with end stage renal disease (ESRD) are increased risk of death from cardiac causes. But prevalence of CVD is increased among all patients with CKD and not only in those with ESRD. That is the, prevalence of left ventricle hypertrophy (LVH) increases as the glomerular filtration rate declines and as many as 30% patients reaching ESRD already have clinical evidence of ischemic heart disease or heart failure. Furthermore, it is important that patients with a reduced glomerular filtration rate are more likely to die of CVD than they are to develop ESRD. These data therefore, reinforce the need to intervene in the earlier stages of CKD, to both prevent and treat CVD.[4,5] The prevalence of angiographically significant coronary artery disease (CAD) ranges from 51-84% depending upon the 6th stage of CKD, peaking in end stage renal disease patients and longstanding diabetes. It has been estimated that the risk of cardiac death in dialysis patients younger than age 45 is hundred times greater than that the general population. Therefore, the present study was conducted to study cardiovascular risk factors in patients of chronic renal failure and to see its correlation with various clinical, radiological and biochemical parameters.[3,6]

This was a prospective study for 6 months. A total number of 60 patients with age ranging from 21 to 60 years were enrolled. There were 45 males and 15 females. The mean age of the patients in group I was 36.1±11.78, in group II was 40.8±11.81 and in group III it was

44±11.75.

Of the 60 patients selected for the study, the maximum number of patients had renal failure secondary to diabetic nephropathy (31%) followed by hypertensive nephropathy (28%), chronic glomerulonephritis (10%), polycystic kidney disease (9%), nephrotic syndrome (9%).

Diabetic nephropathy is also a leading cause of renal failure worldwide. It is also one of the most significant long term complications in terms of morbidity and mortality for individual patient with diabetes. Nearly 30% of chronic renal failure in India is due to diabetic nephropathy.[3,7]

Anemia was common in all the groups. The mean basal hemoglobin level in group I was 10.9±2.1, in group II it was 8.6±1.9 and in group III it was 6.8±1.54. Anemia was present in all the groups, more so in group II and III. Thus, the severity of anemia was related to the duration and extent of kidney failure. The lowest hemoglobin levels are found in those with commence dialysis at very severely decreased levels of kidney function. Foley et al showed that a low level Hb (<8.8 g/dl) was a risk factor for all cause mortality in univariate analysis. The same study showed that anemia was independently associated with a greater risk for LV dilatation, cardiac failure and death. Anemia also appears to be associated with CVD in early stages of CKD.[9-11]

The basal blood urea level in group I was 106.3±70.8, in group II it was 160.5±65.6 and in group III it was 221.3±50.5. The blood urea levels were persistently high in group II and III patients. In patients of group III, who were mostly on regular maintenance dialysis, the blood urea remained persistently high throughout the study. The basal value of serum creatinine in group I was 1.7±0.8, in group II it was 3.6±1.5 and in group III it was 5.7±2.5. The serum creatinine levels were persistently high in group III, indicating the increasing severity of disease.

The basal value of serum uric acid in group I was 7.0±2.3, in group II it was 8.4±2.4 and in group III it was 8.9±2.6. Serum uric acid levels were raised in group II and group III.

The basal value of serum calcium in group I was 9.2±0.84, in group II it was 8.0±0.84 and in group III it was 7.8±1.1. The serum calcium levels were significantly less in group II and group III when compared with group I. The basal value of serum phosphate in group I was 4.6±1.3, ingroup II it was 6.5±2.3 in group III it was 7.5±1.4. The levels were significantly more in group III followed by group II and I, indicating altered calcium and phosphorous metabolism in CKD according to severity of disease. Altered mineral metabolism is responsible for increased coronary artery calcification and cardiovascular risk in patients of ESRD, mechanism being vascular calcification, stiffening, increased peripheral resistance, decrease coronary perfusion and LVH.[4,11]

The basal value of serum lipoprotein-A in group I was 14.1±8.7, in group II it was 49.2±20.2 and in group III it was 76.7±18.2. Patients in group III had 5 to 10 times higher levels of lipoprotein A as compared to patients in group I. It showed a steady increasing graph with lower values in group I, increasing in group II and highest in group III. Lp(A), being an atherogenic lipoprotein, was associated with both anti fibrinolytic and atherogenic effects. Comparison between group I and group II was also highly significant, which shows that increased Lp(A) levels occurred in early stages of chronic kidney disease (CKD). Since the outcome of patients with increased Lp(A) levels was poor, Lp(A) can be considered a primary risk factor for coronary artery disease. Increased Lp(A) concentrations might significantly contribute to the high risk state for atherosclerosis in the otherwise rather normolipemic patients with ESRD. Median Lipoprotein(A) levels in group of individuals with moderate to severe decrease in kidney function has been found to be greater than that of individuals with presumed normal kidney function and increases the risk of CAD by factor 1.7 then compared to those with normal lipoprotein (A) levels .Lipoprotein is independent risk factor for CAD, complex mechanisms come into play main being inhibition of thrombolysis and initiation of clot formation.[5,11]

CA-IMT in the left common carotid artery at base line was 0.5±0.08 mm in group I, it was 0.7±0.10 in group II and in group III it was 0.8±0.16 mm. The intima media thickness (IMT) was very highly significantly increased in groups II and III as compared to group I. The IMT is at present the best studied sonographic marker for early atherosclerotic vascular wall lesions. A thickening of intima – media complex not only reflects local alterations, mostly of common carotid artery (CCA), but also corresponds to generalised. Measurement of carotid artery intima media thickness with ultrasonography is a reliable, reproductive and non invasive method for detecting and monitoring the progression of atherosclerosis in patients with clinical signs of CVD. Therefore, CA-IMT measurement has been proposed as a method for establishing risk stratification for cardiovascular events in both the general population and the dialysis population.[10,11,14]

Blacher et al showed patients on dialysis with increased stiffness of aorta have a lower probability of survival compared with patients with more elastic vessels. This study also evaluated arterial calcification by ultrasound in four major arteries. Scoring was performed on a scale of 0 to 4, with score 0 indicating absence of calcium in any arteries examined and score 4 indicating that calcification was present in all four arteries. In our study similarly, calcification in the bilateral carotid arteries was much higher in patients of group III as compared to patients in group II and group I. when compared between group II and group III, the later had twice as much number of calcium score than the former. The number of patients showing calcification in group III were also higher than group II. Results are compatible with a study by Braun J which showed that coronary artery calcification scores were approximately 2.5 to 5 fold higher in hemodialysis patients compared with non hemodialysis patients regardless of age group. A progressive increase in calcification score was associated with progressive decrease in survival. In the general population and ESRD patients, the presence and extent of arterial calcifications are independently predictive of subsequent and mortality beyond established conventional risk factors.[10,11,14]

The maximum number of patients having plaques and stenosis were seen in group III (50%), followed by group II (20%). No plaques were seen in patients of group I. Around 8 patients showed plaques in more than one carotid artery.

In this regard, it is known that chronic uremic patients show accelerated atherosclerosis and microangiopathic changes, and evidence exists of vascular calcification in carotid and coronary arteries of young patients on hemodialysis. The most prevalent arterial complicationis occlusion and/or stiffening caused, to a large part, by increased calcium content and extensive calcifications.In the general population and ESRD patients, the presence and extent of arterial calcifications are independently predictive of subsequent CVD and mortality beyond established conventional risk factors.[14,15]

Despite improvement in dialysis technology over the past decade, mortality in ESRD remains high. In addition to mortality, patients with ESRD also experience significantly greater morbidity, including a substantial loss of quality of life. The main cause of mortality and morbidity is CVD with an annual mortality rate of 9% which is 10 to 20 fold than in general population, even when adjusted for age, gender, race and the presence of diabetes mellitus.

Diabetes nephropathy to be the most common cause of CKD, followed by hypertension and obstructive uropathy and chronic glomerulonephritis. Overall, the patients with CKD have a low BMI. Anemia is present in all the patients of CKD. ESRD patients have severe anemia. In patients of ESRD the blood urea and serum creatinine remains persistently high indicating the severity of disease. Serum uric acid levels were also raised with increasing stage of CKD. There is altered calcium and phosphorous metabolism in CKD according to severity of disease. These metabolic derangements are associated with increased cardiovascular risks.

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