CARDIAC INVOLVEMENT IN CHRONIC KIDNEY DISEASE
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ABSTRACT

BACKGROUND
At every stage of CKD, cardiovascular disease is the leading cause of morbidity and mortality with 30 to 45% of patients advancing to cardiovascular complications. (1) The aim of the study was to evaluate the prevalence of systolic and diastolic dysfunction, correlate degree of cardiac dysfunction with severity of chronic kidney disease.

METHODS
Present study was a prospective study of all CKD patients admitted in the department of General Medicine, VIMSAR, Burla between Oct 2013-Nov 2017. They were classified into 2 groups. Group B patients with mild to moderate CKD (N= 80) with serum creatinine (1.6-6 mg/dL), Group C patients with advanced CKD (n= 80) with serum creatinine (>6.0 mg/dL). Group A (No=80) taken as healthy controls.

RESULTS
160 cases of chronic kidney disease in the age group of 16-75 years were included in the present study. The male/female ratio was 3:1. In Group B, maximum patients were in age group 56-75 years and in Group C, the age group was 36-55 years. In severe CKD (Group C), the no. of cases of left ventricular hypertrophy (LVH) along with systolic dysfunction (7.5%) was higher than mild to moderate CKD (Group B) which was 2.5%. LVH along with diastolic dysfunction in severe CKD (Group C) was 66 (82.5%) which was higher than mild to moderate CKD (Group B) 44 (55%). LV diastolic dysfunction was more prevalent than systolic dysfunction. In diabetic CKD patients, LV dysfunction was predominantly diastolic irrespective of the degree of LV hypertrophy. Diabetes mellitus was the commonest cause of CKD. Anaemia, Hypertension and LVH was the predominant co-morbidity and detected in most of the patients.

CONCLUSIONS
In the present study, it was observed that the systolic function was well preserved in majority cases of CKD, whereas diastolic dysfunction was more common in CKD patients. Hence, cardiac evaluation should be performed early and aggressive measures should be taken to prevent or delay further progression to reduce cardiovascular morbidity and mortality. Anaemia and Hypertension being major co-morbid conditions contributing to LVH should be detected and treated early.

KEYWORDS
Cardiovascular Involvement, Chronic Kidney Disease, Echocardiography


BACKGROUND
Chronic kidney disease is one of the major global health problems. CKD encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR).¹² It comprises either glomerular filtration rate (GFR) <60 ml/min/1.73 m² for more than 3 months, or kidney damage, including abnormalities or markers of kidney damage, including abnormalities in blood, urine tests or imaging studies. Death from CV risk is 8-fold higher in CKD patients.³⁵

Worldwide ultimate prevalence of CKD in stage 3-5 is around 33 million. The prevalence of CKD in stage 1-4 in the most recent NHANES (National Health and Nutritional Examination Survey) between 1999-2006 was 26 million (13%) out of 200 million United States residents. The United States renal data system estimates that nearly half million patients in the United States were treated for ESRD in 2004 and 2010. (USRDS) Annual Data Report; Bethesda 2010, shows changes in demographics of population, differences
in disease burden among racial groups, under recognition of early stages of CKD and risk factors for CKD may explain this growth.

Indian Scenario
The population of India exceed one billion and is projected to become major reservoir of chronic kidney disease like HTN and DM. There are three population-based study in India, reported as the magnitude of CKD. First study showed, prevalence of CKD based on community survey in Chennai in South India was 0.86% in 2005, rural population. The second study, showed prevalence CKD (S. creatinine >1.8 mg/dl) was 0.79% or 7852 per million of populations. In third study from urban population in city of Bhopal, the crude age adjusted incident rates of ESRD were 151 and 232 per million population irrespectively. In Indian Society of Nephrology (ISN), the epidemiological data, registered, shows that, patient first presented to a nephrologist at stage 5 (47.5%), stage 4 (25.5%), stage 3 (19.6%), stage 2 (4.9%), stage 1 (2.5%). The common aetiology of CKD are diabetic glomerular disease, glomerulonephritis, hypertensive nephropathy, autosomal dominant polycystic kidney disease, cystic and tubulointerstitial nephropathy.

Aims and Objectives
To evaluate the prevalence of systolic and diastolic dysfunction, correlate degree of cardiac dysfunction with severity of chronic kidney disease and detect the co-morbid condition associated with chronic kidney disease

METHODS
160 CKD patients, in the age group of 16 years and above, admitted to the Department of General Medicine, VIMSAR, Burla between October 2013 to November 2017 were included. The study population was divided into 3 groups: Group A: Age and sex matched healthy controls (n=80). Group B: Patients with mild to moderate CKD (n=80) (Serum creatinine 1.6-6.0 mg/dL). Group C: Patients with advanced CKD (n=80) (Serum creatinine >6.0 mg/dL). The following patients were excluded from the study: primary valvular heart disease, congenital heart disease and coronary artery disease, to remove from the bias associated with these diseases. Informed consent was taken from all subjects participating in the study. All patients underwent various investigations: CBC, blood sugar, renal and liver function tests, urine analysis, urine culture, lipid profile, HbA1c, electrolytes, chest skiagram, 12 lead ECG, Echocardiography.

All patients underwnt detailed Echocardiography study M mode, 2D- Echo, Doppler study including tissue Doppler and Colour Flow Imaging using the best echocardiography window to study Left Ventricular morphology and function. As our aim was to evaluate prevalence of LV dysfunction if any, the left ventricular ejection fraction (EF) and fractional shortening FS were taken as measures of LV systolic function. EF was determined by measuring left ventricular volumes in apical 2-chamber view and four chamber view.

Left ventricular volumes were measured by Area-length method both in end diastole and in end systole. EF=LVEDV/LVESV/EVEDVX100% The mean EF in normal population is taken as 59.2±6%. EF was considered decreased if it was <50%. Fractional shortening (FS) was determined by measuring left ventricular internal diameter in diastole (LVIDd) and left ventricular internal diameter in systole (LVIDs) by 2D directed M mode ECHO and FS = (LVIDd-LVIDs)/ LVIDd x 100%. Normal range in adults for FS is 35±8%. FS of ≤25% will be taken as index of systolic dysfunction. Diastolic function will be determined by ratio of peak early diastole velocity (E)/ peak atrial filling velocity (A) of LV i.e. (E/A) measured by Doppler echocardiography. Normal E/A ratio: 1.40 ± 0.54. LV diastolic dysfunction will be considered if E/A velocity are found to be ≤0.8. The normal thickness of IVS and LVPW in diastolic is 6 to 12mm. Thickness >12mm indicates presence of left ventricular hypertrophy.

Inclusion Criteria
- Serum creatinine (>1.5 mg/DL)
- At least 3 months of evidence of kidney damage with an abnormal GFR.
- GFR ≤ 90 mL/Min.
- Renal imaging study (USG).

Exclusion Criteria
- Primary valvular heart disease.
- Congenital heart disease.
- Ischemic Heart Disease.

Statistical Analysis
Statistical analysis (P<0.05) done were student T-Text, one-way ANOVA, Post Hock Test (Tuckey's Method). Statistical calculations were done through Epi Info 7 for windows.

RESULTS
Table 1 shows Age and sex distribution and biochemical parameters in three groups. As evident, all the groups were well matched. The Hb level showed a progressive decline with the severity of renal failure. In patients with mild to moderate CKD, the mean systolic and diastolic blood pressure were 158.10±22.31 and 89.26±11.10 respectively. In severe CKD patients, the mean SBP and DBP were 170.50 ± 20.99 and 95.50±14.20 respectively.

The major echocardiography parameters are given in Table 2. As evident the mean left ventricular internal diameter in diastole (LVIDd) and systole (LVIDs) was higher in patients with mild to moderate and severe CKD groups than the controls. As evident, left ventricular ejection fraction showed a progressive decline with increase in severity of renal failure which was statistically significant in comparison to control. Although mean fractional shortening (FS) in the three group was similar, detail analysis revealed impaired FS. Table 3 shows simultaneous occurrence of HTN, LVH, systolic and diastolic dysfunction in three groups. In group B 72 (90%) cases had HTN and 44 (55%) cases had LVH. In group C, 76 cases had HTN and 64 (80%) had
LVH. There were 2 (2.5%) patients in mild moderate groups while 6 (7.5%) patients in severe CKD groups with LVH and systolic dysfunction. In moderate CKD groups there were 44 (55%) and 66 (82.5%) patients in severe CKD group with both LVH and diastolic dysfunction. Table 4 shows relation of HTN, diastolic dysfunction with LVH in patients with DM in 2 groups. Among cases with diastolic dysfunction in group B 44 (84.6%) were non-diabetic and 22 (78.57%) diabetic. Whereas in group C out of 72 cases with diastolic dysfunction, 54 non-diabetic and 18 diabetic.

**Figure 1. Percentage of CKD with DM 30% and without DM 70% Cases**

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Control (n=80)</th>
<th>Mild to Moderate (n=80)</th>
<th>Severe CKD (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ±SD</td>
<td>44.01±17.3</td>
<td>56.3±11.2</td>
<td>52.14</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>64</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Mean Blood pressure</td>
<td>Systolic</td>
<td>12.62±7.56</td>
<td>158.10±22.31</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.10±4.34</td>
<td>89.26±11.10</td>
<td>95.50±14.20</td>
</tr>
<tr>
<td>Biochemical parameters</td>
<td>Blood Urea (mg/dl)</td>
<td>7.78±9.8</td>
<td>80.75±33.28</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.73±0.12</td>
<td>3.4±1.19</td>
<td>9.68±3.34</td>
</tr>
<tr>
<td>Hemoglobin (gm/dl)</td>
<td>12.5±0.67</td>
<td>8.70±2.0</td>
<td>7.60±2.5</td>
</tr>
<tr>
<td>Blood Sugar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting (mg/dl)</td>
<td>91.92±12.47</td>
<td>189.30±51.70</td>
<td>151.10±17.24</td>
</tr>
<tr>
<td>2 hr PPBS (mg/dl)</td>
<td>131.29±33.49</td>
<td>258.84±68.69</td>
<td>151.40±66.27</td>
</tr>
</tbody>
</table>

**Table 1. Age and Sex Distribution and Biochemical Parameters in Three Groups**

<table>
<thead>
<tr>
<th>Group-A (n=80)</th>
<th>Group-B (n=80)</th>
<th>Group-C (n=80)</th>
<th>p-value</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVID-d (CM)</td>
<td>4.12 ± .54</td>
<td>4.32 ± .56</td>
<td>4.46 ± .44</td>
<td>A vs. B = .266</td>
</tr>
<tr>
<td>LVID-s (CM)</td>
<td>2.35 ± .54</td>
<td>2.8 ± .49</td>
<td>3.07 ± .67</td>
<td>A vs. B = .92</td>
</tr>
<tr>
<td>IVSd (CM)</td>
<td>1.24 ± .15</td>
<td>1.4 ± 1.09</td>
<td>1.27 ± .20</td>
<td>A vs. B = .517</td>
</tr>
<tr>
<td>LVpWd (CM)</td>
<td>1.13 ± .107</td>
<td>1.16 ± .236</td>
<td>1.189 ± .269</td>
<td>A vs. B = .524</td>
</tr>
<tr>
<td>EF%</td>
<td>70.86 ± 5.9</td>
<td>67.33 ± 11.76</td>
<td>64.33 ± 5.76</td>
<td>A vs. B = .102</td>
</tr>
<tr>
<td>FS%</td>
<td>36.1 ± 3.4</td>
<td>38.47 ± 6.88</td>
<td>36.9 ± 3.63</td>
<td>A vs. B = .082</td>
</tr>
</tbody>
</table>

**Table 2. Echocardiographic Parameters in Three Groups**

**DISCUSSION**

In the present study of cardiac dysfunction in patients of chronic kidney disease, 160 cases of Chronic kidney disease diagnosed clinically and confirmed by biochemical and imaging studies were included. The criteria of inclusion was based on National Kidney foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification; 2004. The CKD cases were divided into 2 groups B and C. Group B consisted of cases who had serum creatinine level between 1.6 to 6.0 mg/dl and Group C consisted of cases who had serum creatinine level >6.0 mg/dl. There were 80 cases each in Group B and Group C. Maximum number of cases (56-75 years) in Group B than in Group C (36-55 years). As per annual report of, CKD REGISTRY OF INDIA 2011, mean age for a CKD patient is 50 ± 14.6 years. In our study mean age of CKD cases was 56.3 ± 11.2 in Group B and 52 ± 14 in Group C. 52 (65%) were non-diabetic. In group C 20 (25%) were diabetic and 60 (75%) cases non-diabetic. Over all in the study group, 48 (30%) had DM whereas 112 (70%) were non-DM. Hence our findings were consisted with that of CKD Registry of India. As per the annual report, CKD Registry of Indian Society, 2011, 30.3% CKD patients were due to diabetic nephropathy. In group B 28 cases (35%) were diabetic and four main structural abnormality of the heart occur in CKD mainly (i) LV hypertrophy, (ii) expansion of the nonvascular cardiac interstitium leading to intermyocardiocytic fibrosis, (iii) changes in vascular architecture, and (iv) myocardial calcification, which are risk factor for premature cardiovascular death. Both invasive and noninvasive modalities i.e. ECG, 2D-ECHO and radionuclide scans are utilized. Echocardiography is an excellent non-invasive method to delineate details of the anatomy of cardiac cavity, wall dimensions and wall movements. It is now increasingly being used in the assessment of cardiac performance and is invaluable in the demonstration of structural abnormalities such as LVH and pericardial effusion the LV systolic dysfunction appears late in CRF patients. Systolic functions are preserved in HTN & DM patients with uremia. 

In the present study, the mean ejection fraction was calculated.
fraction in patients with mild/moderate CRF and severe CRF groups showed a downward trend but neither of the CRF groups had mean LVEF <50%. These findings are similar to the findings of Raj et al. (1997) who found mean EF in controls to be 60 ± 12.6%, undialyzed CRF patients 55.4 ± 14.4% and in dialysis population 56.8 ± 13.0%. Dangri et al. (2003) found mean EF in controls to be 63.7 ± 5.1% Group B CRF patients 58.1 ± 6.9% and in Group C CRF patients 55.4 ± 9.8%. Ayus et al. (1981) found that predialysis mean LVEF in end stage renal disease (ESRD) patients was 56 ± 2%. Thus, study suggest that LVEF is well maintained in CRF patients as observed in the present study. Among patients in the mild / moderate CRF group, only 4 patients had LVEF<50% while 6 out of 60 patients in severe CRF groups had LVEF <50% which was not significantly different from controls.

In the present study, there was no significant difference in mean fractional shortening among the three group, however in 4 (5%) cases in mild / moderate CRD group, and 6 cases (7.51%) patients in severe CKD group had fractional shortening <25%. In our present study we found mean FS in control 36.1 ± 3.4%, in group B CKD patients 38.47 ± 6.88 and in group C CKD patients 36.9 ± 3.6. Dangri et al. (2003) found mean FS on controls to be 33.3 ± 3.4%, group B CRF patients 33.4 ± 12.6% and in group C CRF patients 33.0 ± 6.0%. Raj et al. (1997) found fractional shortening in CRF not on dialysis to be 31.4 ± 1.1% and in dialysis patients to be 33.3 ± 13.0%, while in controls it was 33 ± 9.3. They also did not find significant difference in the mean fractional shortening between the three groups. In a study by Greaves et al. (1994) as well FS showed a trend from being highest in the controls (36.5 ± 5.6%), intermediate in undialyzed CRF patients (36.2 ± 7.2%), and lowest in the dialyzed patients (29.8 ± 8.9%), LVH is common in moderate to severe renal failure.

In the present study, in patients with mild / moderate CKD, the EF was decreased in 5% cases and fractional shortening was decreased in 2.2% cases. In patients with severe CKD, the ejection fraction was decreased in 7.5% cases and fractional shortening in 7.5% cases only. In a study by Greaves et al. (1994) 13% of patients had LVH with systolic dysfunction in the dialysis patients. In the present study, systolic function was well preserved in patients with mild / moderate and severe CKD which is in concordance with the previous studies done by P. Dangri et al. (2003) Greaves et al. (1994), Harnett et al. (1995), Colan et al. (1987), and Raj et al. (1997). Left ventricular diastolic dysfunction is an important cause of cardiac morbidity in ESRD patients. Diastolic dysfunction appears to be the initial left ventricular dysfunction and might even precede left ventricular hypertrophy. Diastolic heart function is influenced by numerous factors such as myocardial relaxation and compliance, transvalvular pressure gradient, atrial contraction, preload, heart rate, passive elastic properties, respiratory variant, the restraint pericardium and thoracic wall as well as arrhythmias and valve incompetence. Diastolic dysfunction develops in three phase (i) inversion of ratio of peak early to peak atrial velocity curve, with reduced ventricular filling due to ventricular relaxation (ii) pseudonormalisation of E/A flow pattern, following increased atrial and decreased ventricular relaxation, (iii) development of a restrictive pattern with various degree of early atrial flow velocity involvement.

London et al. (1993) reported a significant reduction in E/A ratio in hemodialysis patients as compared to controls. The prevalence of diastolic dysfunction in the present study was found to be 66 patients (73.33%) in mild/ moderate CRF group and 52 patients (86.67%) in severe CRF group. Left ventricular hypertrophy is the single strongest independent predictor of adverse cardiovascular events. In the present study, we found that 44 (55%) patients in mild/ moderate CKD group and 60 (7.5%) patients in severe CKD group had LVH. These results confirm to prevalence of LVH in patients with ESRD from 40% - 80% in various study. Raj et al. had found the prevalence of LVH in undialyzed CKD patients of 45.7% and in patients requiring dialysis is 76.5% which is similar to the present study. Levin et al. showed the prevalence of LVH in pre dialysis, population to be 38.9%. They also demonstrated that the prevalence of LVH increases with progressive decline in renal function.

In Group B out of 52 non diabetic CKD cases 46 (88.46%) cases had HTN. and out of 28 diabetic cases 26 had HTN. In Group C out of 60 non diabetic cases 54 had HTN and out of 28 diabetic cases 20 had HTN. In the present study in Group B we found diastolic dysfunction in 84.6% in non-diabetic CRF patients (78.57%) in diabetic patients. Diastolic dysfunction was associated with LVH in 42.3% non-diabetic and 78.57% diabetic patients. In Group C we found diastolic dysfunction in 90% non-diabetic CKD cases and 90% of diabetic CKD patients. In diabetic CKD patients LV dysfunction was predominantly diastolic.

CONCLUSIONS

Systolic function was well preserved in majority cases of CKD, whereas diastolic dysfunction was more commonly found in CKD patients. Echocardiography should be performed early during course of CKD to detect LV dysfunction and appropriate and aggressive measures should be taken to prevent or delay further progression to reduce cardiovascular morbidity and mortality. Anaemia and hypertension being major contributors of LVH, should be treated early to prevent cardiovascular events. However, these results need to be validated by larger prospective studies to arrive at more conclusive inference regarding cardiac dysfunction in cases of chronic kidney disease.

Abbreviations

- **CKD**: Chronic Kidney Disease
- **CRF**: Chronic Renal Failure
- **DM**: Diabetes Mellitus
- **ESRD**: End Stage Renal Disease
- **ECHO**: Echocardiography
- **EF**: Ejection Fraction
- **FS**: Fractional Shortening
- **Hb**: Haemoglobin
- **HTN**: Hypertension
- **IVSd**: Interventricular Septal thickness at...
end diastole, LVIDd- Left Ventricular Internal Diameter at end diastole, LVIDs- Left Ventricular Internal Diameter at end systole, LVH- Left Ventricular Hypertrophy, LVMi- Left Ventricular Mass Index, NKF- National Kidney Foundation, Non-DM- Non Diabetes Mellitus, PD- Peritoneal Dialysis, PWD- Posterior Wall thickness at end diastole, RWD- Relative Wall Thickness.

REFERENCES


