Original article

Cardiac status in patients of chronic kidney disease: an assessment by non-invasive tools

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Abstract:

Background: Chronic Renal Insufficiency is a major public health problem. Cardiovascular Disease is the leading cause of morbidity and mortality in patients at every stage of Chronic Kidney Disease. There is a 10-200 fold increased risk of cardiovascular disease in those with Chronic Kidney Disease compared to the age and sex matched with general population, depending on the stage of Chronic Kidney Disease. ***Objective***: The objective of the study was to see correlation, if any, of cardiac status and stage of kidney disease. Materials and methods: The study was conducted at M. M. Institute of Medical Sciences and Research, Mullana, Ambala. Thirty patients of Chronic Kidney Disease were included in the study. Chronic Kidney Disease is defined as kidney damage lasting for more than 3 months characterised by structural or functional abnormalities of the kidney, with or without decreased Glomerular Filtration Rate (GFR), according to the K/DOQI Guidelines. Inclusion criteria were based on symptomatology and clinical history of features suggestive of Chronic Kidney Disease. Symptoms, Signs and history of the patients were used to filter out patients who did not fit in the criteria and selected patients on the basis of criteria were further evaluated and investigated. All patients were subjected to detailed history and clinical examination. Patients with age <20 years, with history of Diabetes Mellitus, Dyslipidemia, Intrinsic Diseases of Ventricles, Congenital Heart Disease and chronic smokers were excluded from the study. A standard 12 lead ECG was done in all cases. Echocardiography was done in ECHO lab of Cardiology unit in MMIMSR. Echocardiographic assessment was done by using Model vivid Colour Doppler Echocardiography machine of GE make. Apical four chamber view was employed to obtain the measurements of Left ventricular volume in diastole and systole, Ejection fraction; Left Ventricular Indices were assessed and then were used to calculate Left Ventricular Mass by using the cube formula proposed by Devereux. Patients included in the study were treated as per the standard treatment schedule. The data obtained was analysed with appropriate statistical analysis tools at the end of the study and conclusive evidence was derived. ***Results***: In the present study the mean Left Ventricular Mass was 249.76 ± 69.35 gms with 73% study cases having Left Ventricular Mass more than the reference range, also Left Ventricular Mass showed a progressive rise with increase in S. Creatinine levels. In the present study, Left Ventricular dysfunction was seen in nearly half of the cases while approximately one-fourth cases (23%) also had Systolic Dysfunction. Pericardial Effusion was also observed in 10 % the study cases in the present study. ***Conclusion***: Cardiac functions particularly Left Ventricular parameters. Left Ventricular free wall thickness and Left Ventricular Mass being common abnormality in CKD patients.

Keywords*:* chronic kidney disease; cardiovascular disease; cardiac status; echocardiography

Bangladesh Journal of Medical Science Vol. 15 No. 02 April'16. Page : 207-215

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Introduction:

Chronic Renal Insufficiency is a major public health problem. The number of patients with End Stage Renal Disease has steadily increased over the years. In the United States, the rate has been reported as 6-7% per year[3] In India, the incidence of Chronic Kidney Disease was suggested to be 100 per million populations by single centre studies from tertiary care hospital. Upto 0.8% of the population may suffer from Chronic Kidney Disease thereby putting the number at about 7.85 million of the 1billion population[4].

Effect of chronic kidney disease on cardiovascular system

Cardiovascular Disease is the leading cause of morbidity and mortality in patients at every stage of Chronic Kidney Disease. There is a 10-200 fold increased risk of cardiovascular disease in those with Chronic Kidney Disease compared to the age and sex matched with general population, depending on the stage of Chronic Kidney Disease. Between 30-45% patients of Chronic Kidney Disease reaching stage 5 Chronic Kidney Disease already have advanced cardiovascular complications, so many patients succumb to cardiovascular disease before ever reaching stage 5 Chronic Kidney Disease[12].

Ischemic vascular changes

The presence of any stage of Chronic Kidney Disease is a major risk factor for ischemic cardiovascular disease, including occlusive coronary, cerebrovascular and peripheral vascular disease. The increased prevalence is due to traditional (classic) i.e. Hypertension, Hypervolemia, Dyslipidemia, Sympathetic overactivity and hyperhomocysteinemia and non traditional (CKD related) risk factors like Anemia, Hyperphosphatemia, Hyperparathyroidism, Sleep Apnoea, and generalised inflammation. Coronary reserve, defined as increase in coronary blood flow in response to greater demand is also attenuated. Cardiac Troponin levels are also elevated in Chronic Kidney Disease without evidence of acute ischemia, thus complicating the diagnosis of myocardial infarction in these patients[7].

Peripheral vascular disease

The inflammatory state associated with reduction in kidney function is reflected in increased circulating acute phase reactants, such as inflammatory cytokines and C-reactive protein, with corresponding fall in the negative acute phase reactants such as albumin and fetuin. The inflammatory state accelerates vascular occlusive diseases, and low level of fetuin permits more rapid vascular calcification, especially in the face of hyperphosphatemia.

Heart failure

In Chronic Kidney Disease, abnormal cardiac function secondary to myocardial ischemia, left ventricular hypertrophy, and frank cardiomyopathy, along with salt and water retention often results in heart failure or even episodes of pulmonary edema. A form of low pressure pulmonary edema can also occur in advanced Chronic Kidney Disease, manifesting as shortness of breath and bat wing distribution of alveolar edema fluid on the chest x-ray. This occurs due to increased permeability of alveolar capillary membranes due to uremic state. Other Chronic Kidney Disease-related risk factors, including anaemia and sleep apnoea, may also contribute to risk of heart failure[6].

Hypertension and left ventricular hypertrophy

LVH is highly prevalent in both stages 3 and 4 CKD and dialysis patients and represents a physiologic adaptation to a long term increase in myocardial work requirements[8].

Cardiomyopathy are among the strongest risk factors for cardiovascular morbidity and mortality in patients with Chronic Kidney Disease and, are thought to be related primarily, but not exclusively, to prolonged hypertension and ECFV overload. Also anaemia due to Chronic Kidney Disease can also generate high cardiac output state and subsequent heart failure[11].

Pericardial Disease

Chest pain with respiratory accentuation, accompanied by a friction rub, is diagnostic of pericarditis. Classic electrocardiographic abnormalities include PR-interval depression and diffuse ST-segment elevation. Pericarditis can be accompanied by pericardial effusion that is seen on echocardiography and can rarely lead to tamponade, however, the pericardial effusion can be asymptomatic, and pericarditis can be seen without significant effusion.

Pericarditis is seen in advanced uraemia, and is more often observed in underdialyzed, non-adherent patients than those in those starting and those adherents to dialysis. Pericarditis is frequently seen in peritoneal dialysis patient than it occurs in haemodialysis patient[10].

Arrhythmias

Arrhythmias are very frequently seen in elderly during dialysis because of metastatic complication, amyloidal infiltration, coronary heart disease, cardiac hypertrophy, and hypertension are more

frequent than in younger patients. Uraemia, hyperkalemia, acidosis and disorders of calcium-phosphate balance have been associated with higher rates of supraventricular and ventricular arrhythmias. Due to presence of conditions like left ventricular hypertrophy, left ventricular dilation, heart failure and valvular diseases, higher rates of almost all arrhythmias are seen in Chronic Kidney Disease, including bradyarrythmias and heart block[12].

Objective:

The objective of the study was to see Correlation, if any, of cardiac status and stage of kidney disease.

Materials and methods:

The study was conducted at M. M. Institute of Medical Sciences and Research, Mullana, Ambala. Thirty patients of Chronic Kidney Disease were included in the study. The patients taken from Outpatient department (OPD) and Indoor wards of the department of Medicine and Emergency Department. Chronic Kidney Disease is defined as kidney damage lasting for more than 3 months characterised by structural or functional abnormalities of the kidney, with or without decreased Glomerular Filtration Rate (GFR), according to the K/DOQI Guidelines1.

Inclusion criteria

Inclusion criteria was based on symptomatology and clinical history of features suggestive of Chronic Kidney Disease. Symptoms, Signs and history of the patients were used to filter out patients who did not fit in the criteria and selected patients on the basis of criteria were further evaluated and investigated.

All patients were subjected to detailed history and clinical examination All patients were subjected to following investigations at the beginning of the study, like -

1. Complete Blood Count
2. Urine complete examination
3. Fasting Blood Sugar
4. Lipidogram
5. HbA1c - done by Ion Exchange Resin Method.
6. Blood urea and Serum Creatinine
7. Chest X Ray- PA view
8. Electrocardiography - 12 lead ECG was recorded on ECG machine of BPL make, Model no. CARDIART 108T-DIGI.
9. Echocardiography - Echocardiographic assessment was done using an ultrasound system Model VIVID-e COLOUR DOPPLER Echocardiography machine of GE make with a 3.5 MHz transducer frequency for M-Mode and 2.5 MHz for Doppler recording.
10. Written and informed consent from all the patients were taken

Staging of chronic kidney disease

Chronic Kidney Disease has been divided into five stages based on guidelines of the National Kidney Foundation [Kidney Dialysis Outcome Quality Initiative, KDOQI] depending on the estimated GFR (eGFR).2

Stage	GFR (ml/min/1.73m2)	Description
0	>90	Kidney injury with normal GFR but with risk factor for CKD
1	≥ 90	Kidney injury with normal GFR with Kidney Damage like protienuria, abnormal urine sediment etc.
2	60-89	Kidney injury with mild reduction in GFR
3	30-59	Kidney injury with moderate reduction in GFR
4	15-29	Kidney injury with severe reduction in GFR
5	<15	End-Stage Renal Disease

Glomerular Filtration Rate (G.F.R.) was calculated using

Cockcroft-gault equation

$$\text{Estimated Creatinine clearance (ml/min)} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{72 \times \text{S.Creatinine (mg/dl)}}$$

For females, multiply by 0.85

Exclusion criteria

Patients with the following diseases were excluded from the study

1. Patients with age < 20 years of either sex.
2. Patients with History of Hypertension or on Anti-Hypertensives (before developing symptoms and signs of Chronic Kidney Disease)
3. Patients with Diabetes Mellitus (HbA1c > 6.5%, Fasting Plasma Glucose > 126 mg/dl)
4. Patients with history of Dyslipidemia (deranged

Serum Lipid Gram) before symptoms and signs of CKD
5. Patients with Intrinsic Diseases of Ventricles
6. Patients with Congenital Heart Disease.
7. Chronic Smoker.

1. **Clinical Features :**

a. History: a detailed history regarding duration of illness, any treatment received and past history of illness was taken. Age and sex of the patient was noted.

b. General Physical Examination: a detailed general physical examination was done with special reference to pulse rate and character, blood pressure, jugular venous pressure, presence of pallor, clubbing or pedal edema.

c. Respiratory and Cardiovascular Examination: a thorough examination of chest and CVS was done with emphasis of features of emphysema and evidence of left ventricular overload i.e. shortness of breath, pulmonary edema, orthopnoea and paroxysmal nocturnal dyspnoea, soft first heart sound, apex beat displaced outwards, heave often present, high pitched pan-systolic murmur at the apex, radiating to the back or clavicular area etc.

2. **Chest Roentgenogram**

Posteroanterior films were obtained in all subjects. The following parameters were noted:
- Low, flat or irregular diaphragm
- Air trapping or bullae
- Increased transradiancy
- Main pulmonary artery shadow enlargement
- Prominent bronchovascular markings
- Cardiomegaly/ narrow heart shadow
- Increased distance between intercostal spaces
- Pleural Effusion - unilateral/ bilateral.

3. Electrocardiography (ECG)

A standard 12 lead ECG was done in all cases. Abnormalities on the ECG often provide the first evidence of cardiac dysfunction in patients in whom it is suspected. Diagnosis of LVH on electrocardiogram was made using Romhilt-Estes point score system95.

4. Echocardiography

Echocardiography was done in ECHO lab of Cardiology unit in MMIMSR. Echocardiographic assessment was done by using Model vivid Colour Doppler Echocardiography machine of GE make. Patients were examined in the left lateral and supine position in quiet respiration.

a. M Mode Echocardiography

Left ventricular dimensions were obtained by directing the ultrasonic beam at the chamber between the mitral valve echoes and papillary muscle echoes in the left parasternal long axis view. Following measurements were made:-
- Left ventricular internal diameter in diastole and systole
- Interventricular septum thickness in diastole and systole

b. Two Dimensional Echocardiography

Apical four chamber view was employed to obtain the measurements of

Left ventricular volume in diastole and systole , Ejection fraction, Left Ventricular Indices were assessed and then were used to calculate Left Ventricular Mass by using the cube formula proposed by Devereux[31].

LV Mass = Myocardial Volume x 1.05 g/cm3 = [(IVSd + LVIDd + LVPWd)]3 - (LVIDd)3 x 1.05 g/cm3.

Patients included in the study were treated as per the standard treatment schedule. The data obtained was analyzed with appropriate statistical analysis tools at the end of the study and conclusive evidence was derived.

The study was ethically approved by ethical committee of M.M.Insttitute of Medical Sciences & Resarch, Mullana (Ambala), India.

Observations:

The study was conducted at M.M. Institute of Medical Science and Research, Mullana, Ambala. Thirty patients of Chronic Kidney Disease satisfying the Inclusion criteria were taken from Outpatients department, Indoor wards of department of Medicine and Emergency department. These patients were then subjected to Clinical examination and routine investigations along with some special investigations like Echocardiography.

The observations hence made have been tabulated and presented as follows.

Table 1: Showing age and gender distribution of patient's age (in years)

Age (in years)	Male	Female	Total
21 -30	3	1	4 (13.3%)
31-40	4	3	7 (23.3%)
41-50	3	3	6 (20%)
51-60	5	3	8 (26.7%)
61-70	1	0	1 (3.3%)
71-80	3	1	4 (13.3%)

Although the females were only 11 of the total 30 patients studied (33%), but the number of female patient in the age group 31 - 60 years, was not

grossly different to their male counterpart of the same age group (9:12). Also maximal number of patients (70%) fell in the age group of 31- 60 years.

Table 2: Showing duration since diagnosis in patients of CKD duration since diagnosis

	Number	**Percentage (%)**
<6 Months	15	50
≥6 months - 1 year	5	16.7
≥ 1 year - 2 years	4	13.3
≥ 2 years	6	20

Duration of the disease was variable but 50% of study subjects had the disease for more than 6 month.

Table 3: showing s. Creatinine levels in CKD

Patients s.creatinine (mg/dl)	**Number**	**Percentage (%)**
< 6	2	6.7
6.1 - 10	18	60
> 10	10	33.3

Creatinine value was more than 6mg/dl in most of the study patients – 93.3%.

Table 4: showing ECG findings in patients with CKD

Observation	**Number**	**Percentage (%)**
LVH	23	76.7
LVH + Tall T	4	13.3
LVH + Prolonged QT interval	2	6.7
LVH + Tall T + Prolonged QT interval	1	3.3

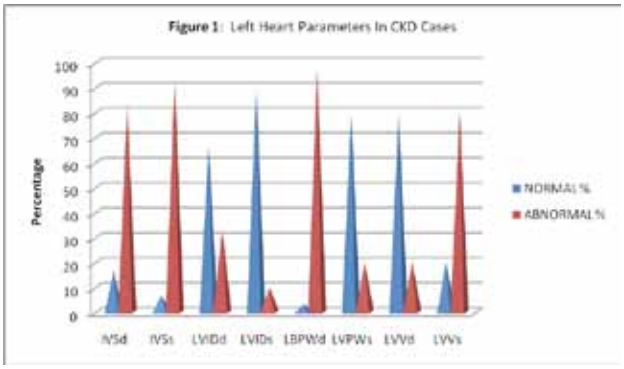
ECG abnormalities were present in all cases. Left Ventricular Hypertrophy present in 100% study subjects; while in 23.3% patients LVH was associated with changes suggestive of Dyselectrolytemia (Hyperkalemia).

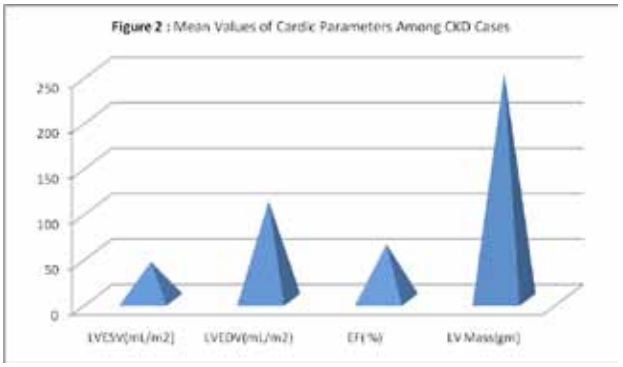
ECG abnormalities were present in all cases. Left Ventricular Hypertrophy present in 100% study subjects; while in 23.3% patients LVH was associated with changes suggestive of Dyselectrolytemia (Hyperkalemia).

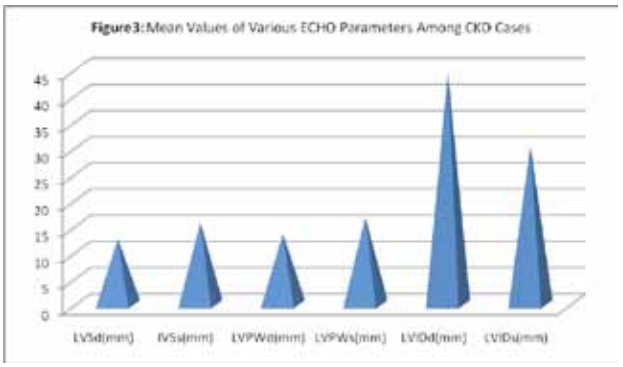
The Thickness of IVSd and LVPWd were higher than normal but it was the Left Ventricular Mass which was significantly increased confirming Left ventricular Hypertrophy. However the Systolic and diastolic functions of Left ventricle were normal.

Table 5: Showing mean values of various echo parameters

PARAMETRES	MEAN VALUES	STANDARD DEVIATION
IVSd (mm)	12.55	±1.33
IVSs (mm)	15.65	±2.20
LVPWd (mm)	13.51	±6.42
LVPWs (mm)	16.69	±1.78
LVIDd (mm)	44.43	±7.26
LVIDs (mm)	30.42	±6.04
LVESV (mL/ m2)	41.78	±17.43
LVEDV (mL/m2)	103.82	±25.78
EF (%)	61.12	±7.82
E:A	1.08	±0.55
LV mass (gm)	249.76	±69.35







Discussion:

The present study was conducted in Department of Medicine at MMIMSR Hospital, Mullana. Thirty Chronic Kidney Disease patients were selected and detailed echocardiography was done. The results obtained were compared to Normal values for any abnormalities in Cardiac functions.

The study included thirty patients of CKD with age ranging from 20 years to 80 years. CKD was most prevalent in the age group of 31 - 60 years. In the study youngest patient was of the age of 22 years while oldest was of 76 years. The mean age of the study was 47.7 ± 15.10 years, which was comparable to 51 ± 17 years in a study by Foley et al [17] and 52.9 ± 15.9 years in a study by McCullough et al [12], and 41 ± 12.1 years in a study by Singh NP et al [25]. The mean duration of CKD in present study was observed to be more 6 than months as seen in about 50% study cases.

The Male: Female ratio was 1.72:1, comparable to 1.81:1 in a study by Foley et al70 and 1.8:1 in a study conducted by Singh NP et al [25].

The mean Blood Urea levels in the present study were 130.44 ± 24.97 mg/dl. This was comparable to Blood Urea levels of 121.2 ± 30.26 mg/dl in a study conducted by Singh NP et al [25] and 117 ± 15.3 mg/dl in a study conducted by Foley et al [17]. The mean S. Creatinine values were 10.33 ± 4.95 mg/dl in the among the study cases of CKD in the present study.

In the present study, Hemoglobin levels were below 10 gm/dl in all the patients (except 1). More than one-third of the patients had Hemoglobin levels below 7gm/dl, thereby emphasising the need for correction of Anemia in patients of CKD. This was comparable with the study by Foley et al [17] having mean Hemoglobin levels of 8.4 ± 1.7 gm/dl in CKD patients and 5.45 ± 2.26 gm/ dl in a study by London GM [25] .

In present study, mean S. Potassium levels in CKD patients 5.54 ± 0.54 mEq/ L. This was comparable to S. Potassium levels of ≥ 5 mEq/ L in studies conducted by Singh NP et al [25] and Hayes et al [20].

If LVHis detected on ECG it usually means that an advanced degree of cardiac involvement has already occurred. ECG is inexpensive, easy to perform and provides additional prognostic information. In this study the Romhilt-Estes Point score system [27] was used to find the prevalence of LVH in CKD patients. Subjects having a score of 5 or more points were considered to have LVH in Hypertensive subjects. In the present study all the cases had ECG changes, with LVH present unanimously in all the ECGs. In almost 1/4th of the patients (23%) it had changes associated with Hyperkalemia viz- Tall tented T-waves, prolonged QT interval. The ECG changes were in confirmity with those in study conducted by Stewart GA et al [9], who observed > 80% had LVH, also prolonged QT interval was found associated with poor Renal function, these features were also comparable to another study by Makusidi et al [19] who observed ECG changes in patients of CKD with LVH, Left Atrial Enlargement and other changes in 86% patients in his study.

Cardiomegaly and Pleural Effusion bilaterally was also observed in Chest X Rays of the study cases of CKD in the present study. Cardiomegaly was seen in majority of the cases (93.3%) and was frequently (33%) associated with bilateral Pleural Effusion on the study of C X-rays. This was comparable with the study carried by M Golshan et al [24] who found CKD as a cause of pleural effusion in 6 of 106 patients with transudative pleural effusion in his study involving 213 patients with pleural effusion. This observation was also backed by another study conducted by Ray S et al [23] whose study had CKD, uremic pleural effusion accounted for 19% of the total pleural effusion cases studied by them.

Left ventricular echo parameters

In the present study, majority of the study cases showed LVH on echocardiography. This was comparable to the study conducted by Foley et al among the patients of Chronic Kidney Disease [15,17]. LVH is defined as an increase in Left Ventricular Mass, which was detected by echo in patients of CKD . In the present study the mean Left Ventricular Mass was 249.76 ± 69.35 gms with 73% study cases having Left Ventricular Mass more than the reference range, also Left Ventricular Mass showed a progressive rise with increase in S.Creatinine levels. This was comparable to study conducted by Foley et al [15, 17] and Angela Wang et al [29]who on performing echocardiography in patients of CKD found high prevalence of LVH in them.

The mean thickness of Inter Ventricular Septum in diastole (12.55 ± 1.33 mm) and systole (15.56 ± 2.20 mm) was significantly increased than the normal reference range in cases of CKD in present study, which was comparable with the study results by Agrawal et al [16](IVSd- 13 ± 3.0 mm, IVSs- 15±3.0mm) and Yildiz et al58 who in their study observed significantly higher Interventricular Septum thickness (IVSd- 13 ± 3.6 mm).

Left Ventricular Internal Diameter in systole in

the study was 30.42 ± 6.04 mm and diastole in patients of CKD was 44.43 ± 7.26mm, both internal diameters were well within normal limits, this was comparable with those in study conducted by Agrawal S et al [16](LVIDs- 27 ± 0.7 mm, LVIDd- 40 ± 0.7 mm), where the Left Ventricular Internal Diameter was also within the normal reference range. However increase in diameter was observed with increasing severity of CKD among cases. Shah et al [22], in their study also had similar observations (LVIDs- 37.46 ± 6.6 mm, LVIDd- 50.34 ± 15.7 mm).

In the present study, the Left Ventricular Posterior Wall thickness in diastole was 13.51 ± 6.42 mm and in systole was 16.69 ± 1.78 mm, which was higher than the normal reference range. This was in conformity with the thickness of posterior wall in diastole 12.75 ± 0.2 mm as studied by Agrawal et al [16].

In this study, majority of the patients showed LVH as evident by increase in Left Ventricular Mass. Left Ventricular Mass was calculated by using Devereux Regression [25]. Left ventricular Mass was found to be significantly increased as was evident by increase in thickness of Interventricular Septum in diastole and Left Ventricular Posterior Wall thickness, with the increase in severity of the disease. This was comparable to observations in the study conducted by Meyeon P et al [30], who documented an increase in Left Ventricular Mass with increase in severity of the disease in CKD patients. The present study results are also comparable to study by Farshid A et al [18] and Foley et al [17] who also demonstrated an increase in Left Ventricular Mass in their studies involving CKD patients.

In the present study, Left Ventricular dysfunction was seen in nearly half of the cases while approximately one-fourth cases (23%) also had Systolic Dysfunction. This was similar to findings of Systolic Dysfunction with LVH in study conducted by Kale et al60. Agrawal S et al [16], also observed Left Ventricular dysfunction and Systolic Dysfunction in their study among CKD patients. However a higher prevalence of Diastolic Dysfunction among CKD patients was observed by Foley et al [17] in their study.

Pericardial Effusion was also observed in 10 % the study cases in the present study. The prevalence of Pericardial Effusion in CKD patients similar with study by Kleiman JH et al [21]who observed Uremic Pericardial Effusion in 6% among their study cases who had pericardial effusion more than 100ml and concluded CKD as one of the cause of Pericardial Effusion.

Conclusion:

Chronic Kidney Disease is a fairly common disease with almost comparable preponderance in either of the sexes. Etiology being multifactorial, fairly good proportion of CKD patients has etiology like Chronic Glomerulonephritis, Autosomal Dominant Polycystic Kidney Disease, other than common etiology of Hypertension and Diabetes Mellitus. Kidney and Heart have curious relationship. Kidney is one organ which many be the cause of hypertension and it is also the organ which suffers most with the effects of hypertension. Hypertension is one of the leading disease causing increased cardiac morbidity and mortality. The disturbed Renin-Angiotensin System in CKD largely affects the cardiac physiology. Cardiac functions particularly Left Ventricular parameters. Left Ventricular free wall thickness and Left Ventricular Mass being common abnormality in CKD patients. Increase in severity of the disease with increasing levels of S. Creatinine and changes in Left Heart geometry as assessed on echocardiographic examination have a direct correlation. ECG is quick, cheap and readily available investigation to document Left Ventricular Hypertrophy but Echocardiography is a better option.

Echocardiography is a sensitive, non-invasive and affordable modality to assess cardiac functions in Chronic Kidney Disease patients. Electrocardiogram and Chest radiography are good tools to document changes in anatomy and effects on coronary circulation, but Echocardiogram remains an excellent tool for functional assessment which takes the main stay of therapeutic decision and prognostic assessments and should be used regularly in all patients of CKD for early detection of cardiac dysfunction.

Acknowledgement:

The authors thank the patients for their consent to participate in the study and wish to acknowledge for every the support from M. M. Insttitute of Medical Sciences & Resarch, Mullana (Ambala), India for supporting to conduct the study.

Conflict of interest: None declared.

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