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A Study on Prevalence of Asymptomatic Cardiac Abnormalities in Patients with Chronic Tubulo Interstitial Syndrome by Echocardiography

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ABSTRACT

Chronic kidney disease (CKD) is said to be the presence of renal damage with or without compromised renal function. Chronic renal failure (CKD) affects almost all systems of the body and results in various abnormalities, leaving significant morbidity and mortality. Of the various causes, infection and cardiovascular events contribute towards a large proportion of its occurrences. The most common cause of death in Chronic Kidney disease patients is due to cardiovascular disease. Left ventricular hypertrophy and Coronary artery disease are considered to be the two major cardiovascular disorders among CKD patients. The present study is aimed at assessing the prevalence of cardiac abnormalities among the asymptomatic chronic tubulointerstitial syndrome (CTIS) patients by echocardiography. The parameters studied to detect the cardiac abnormalities are Regional Wall Motion Abnormality (RWMA), Interventricular wall thickness (IVWT), Posterior ventricular wall thickness (PVWT), Ejection Fraction (E.F.), Fractional Shortening (F.S.), E/A ratio, Valvular lesions, Pericardial Effusion. Of the above parameters, Interventricular wall thickness, Posterior ventricular wall thickness, Ejection Fraction, Fractional shortening and E/A ratio had significant association among the patients with asymptomatic CTIS. Left ventricular hypertrophy was observed among 64.7% of the patients. Ejection fraction <50% is seen among 83.8% of the study population, 83.8% had abnormal E/A ratio, and 67.6 % had abnormal fractional shortening. In conclusion, CTIS in various stages of CKD has asymptomatic echocardiographic abnormalities which have to be kept in mind as it has an impact on mortality and morbidity.

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INTRODUCTION

The increased cardiovascular risk associated with all stages of CKD has been well established (Foley *et al.*, 1998). On an average, the estimated mortality rates due to cardiovascular causes are 10 to 100 fold higher among patients on dialysis than age and sex-matched individuals in the general population (Muntner *et al.*, 2005). Many of the standard cardiac risk factors which were documented in the general population will contribute to cardiac risk in CKD patients. The prevalence of Framingham's risk factors is more in individuals with CKD than those with normal renal function (Muntner *et al.*, 2005). Besides, rare risk factors which are common among

CKD patients also contribute to the liability of cardiovascular disease.

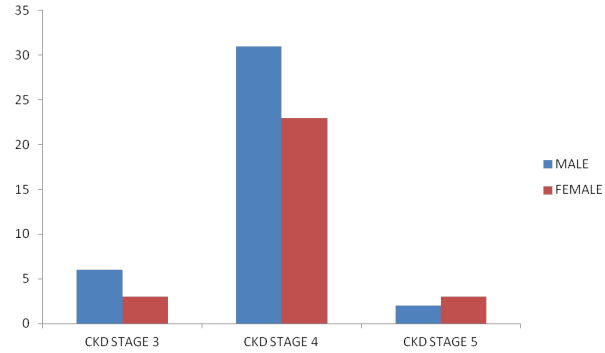

Figure 1: Sex Distribution in the study population

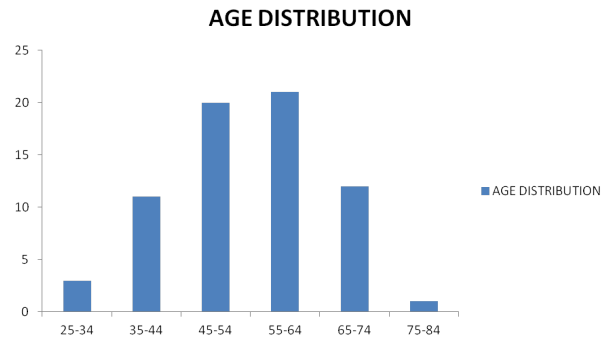

Figure 2: Age distribution in the study population

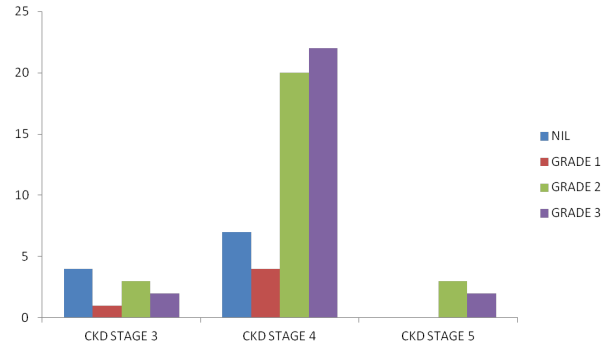

Figure 3: Diastolic Dysfunction in various stages of CKD

Hypertension is one of the many common cardiovascular risk factors that add to the cardiovascular risk associated with CKD (Muntner *et al.*, 2005). Diabetes is linked with adverse effects in all the stages of CKD. The presence of LVH (Bullock *et al.*, 1984), an obstacle that increases in proportion to the worsening eGFR is also a cardiovascular risk factor in CKD patients (Kestenbaum *et al.*, 2005). Smoking and Tobacco usage is linked with higher mortality and incidence of heart failure amongst patients

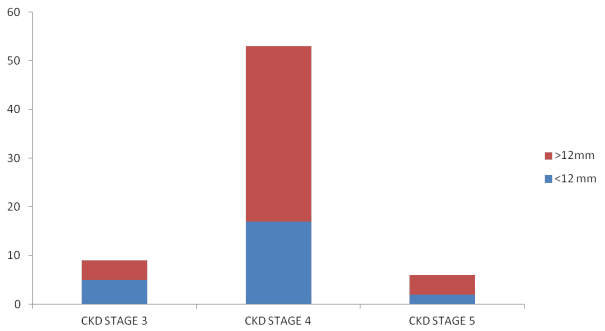

Figure 4: Inter ventricular thickness in various stages of CKD

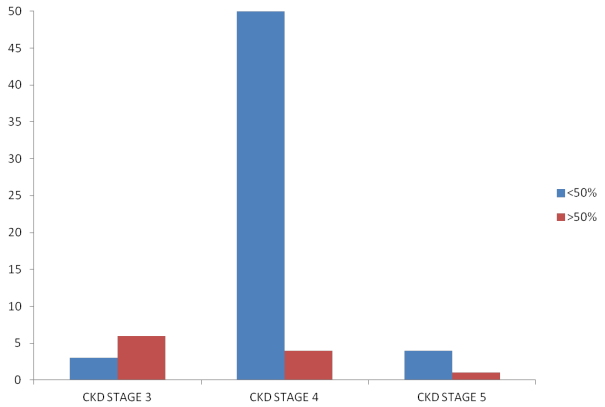

Figure 5: Ejection Fraction in the study group

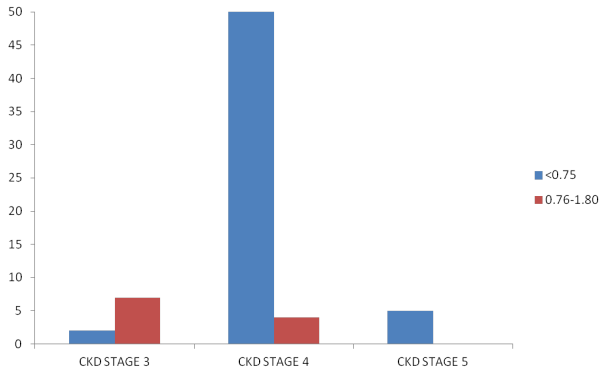

Figure 6: E/A Ratio in the study group

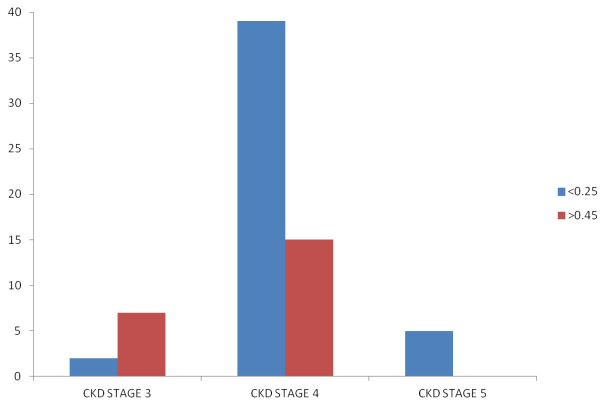

Figure 7: Fractional Shortening in the study group

Table 1: Echocardiographic abnormalities in the study group

Echo Abnormality	Number of Cases	Percentage
LVH	44	64.7%
F.S (<25%)	41	60.2%
E.F (<50%)	57	83.8%
E/A (<0.75/ >1.8)	57	83.8%
RWMA	3	4.4%

with stage5 CKD (Levin *et al.*, 1996). Numerous cardiac risk factors linked with CKD are exclusive (non-traditional risk factors) (Levey *et al.*, 1998). Anaemia is a risk factor for antagonistic cardiovascular consequences in CKD patients. Abnormal parathyroid hormone levels, serum phosphate levels, calcium-phosphate binding product, poorly controlled metabolic bone disease are separate cardiovascular risk factors in the CKD stage 5 (Block *et al.*, 1998). These lead to arterial calcification, arteriosclerosis and increased vascular wall stiffness. Aortic stiffness is a separate prognostic marker of coronary artery disease (Tonelli *et al.*, 2005). Inflammation is one of the non-traditional risk factors which is alleged to have a role in facilitating cardiovascular risk in CKD patients. Proteinuria is associated with an increased risk of cardiovascular disease (Hoehner, 2002). Congestive cardiac failure (CCF) is most likely to develop in CKD patients (Parfrey *et al.*, 1990). Renal damage confers a significant clinical risk for increased mortality in patients with heart failure (Smith *et al.*, 2006).

The chronic tubulointerstitial syndrome is a clinical entity where all the CKD patients who are non-hypertensive, non-diabetic, non-proteinuria are included (Soubassi *et al.*, 2007). It is a likely diagnosis of underlying chronic tubulointerstitial nephritis which presents as a slowly progressive renal impairment.TIN is a significant cause of renal dysfunction and end-stage renal disease (ESRD). The most common causes of TIN were analgesic abuse, urinary tract obstruction, nephrocalcinosis and hyperuricemia. The pathogenesis by which numerous etiologies mediate renal tubulointerstitial injury can be either direct cytotoxicity or indirectly induction of systemic inflammatory or immunologic reactions (Palmer, 1997). In any patient with unexplained renal failure with or without specific tubular dysfunction consider a probable diagnosis of TIN. Clinical Findings include Hyperchloremic metabolic acidosis, Hyperkalemia, Reduced maximum urinary concentration ability (polyuria, nocturia), Partial /Complete Fanconi's syndrome comprising of Phosphaturia, Bicarbonaturia, Aminoaciduria, Uricosuria, Glycosuria and Urine analysis showing few cellular elements. Suspected TIN patients require full workup including occupational histories, clinical examination and clues offered by the initial workup.

Materials And Methodology

This study aims to find a prevalence of asymptomatic echocardiographic abnormalities amongst the chronic tubulointerstitial syndrome patients.

Objective

To identify patients with a chronic tubulointerstitial syndrome without any symptomatic cardiac abnormalities by echocardiography. To study the correlation between echocardiographic abnormalities and severity of chronic kidney disease. The present study was a prospective study done from June 2017 to June 2018, on patients who visited Saveetha Medical College, Chennai, a tertiary care referral hospital with a clinical diagnosis of CKD. The study protocol was approved by the Institutional Ethics Committee, Saveetha Medical College and informed specific consent in written was obtained before enrolment in the study from the patient.

Based on the existing literature, (by allowing alpha error of 5%, a beta error of 20% (power 80%) for a relative precision of 20% at 5% significant level the estimated sample size to be studied was calculated to be 64 patients. The following were the inclusion criteria in the present study - age above 18 years, both sexes, with the clinical diagnosis of Chronic Tubulo Interstitial Syndrome (defined as non-diabetic, non-hypertensive, non -proteinuric Chronic Kidney Disease) confirmed by clinical (nephrologist) and/or by biochemical evidence. The following groups of patients were excluded from the study, Patients with Acute Kidney Injury (AKI), Cardiomyopathies, Established proteinuria, Ischemic heart disease, Congenital heart disease, Rhythm abnormalities due to dyselectrolytemia, established valvular heart disease, Diabetes and Hypertension. Necessary demographic details like name, age, sex and discipline of the study were collected. Urine analysis (protein, sugar, ph, microscopy), Blood analysis (complete blood count, differential count, lipid profile, fasting and

postprandial glucose levels, urea, creatinine, uric acid, electrolytes, calcium, phosphorus), Chest X-ray, Ultrasound kidney ureter and bladder (KUB), Multichannel ECG (12 leads) were done.

eGFR calculated by CKD-EPI formula (2009) (Stenvinkel, 2003; Parfrey, 2000). GFR = 141 X min (Scr/κ, 1)$^{\alpha}$ X max(Scr/ κ, 1)$^{-1.209}$ X 0.993^{Age} X 1.018 [if female] X 1.159 [if black]; where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α i s –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

In echocardiographic evaluation, the participants will be subjected to 2Dechocardiography and M mode with a 3.5 MHz transducer probe. The M mode recording perpendicular to the long axis of the left ventricle and through the centre of the left ventricle at the papillary muscle level was taken as a standard measurement of systolic and diastolic wall thickness and chamber dimensions. The left ventricular ejection fraction(E.F.) and fractional shortening(F.S.) were taken as left ventricular systolic function. The diastolic function will be estimated by measuring E/A ratio (E is peak early diastolic velocity and A is peak atrial filling velocity of left ventricle across the mitral valve) E/A rate less than 0.75 and more than 1.8 will be deliberated as diastolic dysfunction. LVH will be diagnosed when interventricular septum thickness or left ventricular posterior wall thickness was $\geq$12 mm. The details of the patient, history, lab investigations, echo findings are tabulated in a semistructured-questionnaire form and are subjected to statistical analysis.

RESULTS AND DISCUSSION

The present study was undertaken for evaluating the asymptomatic echocardiographic abnormalities among chronic tubulointerstitial syndrome patients. The data was collected and analysed. All the statistical analysis were completed using Statistical Package for Social Science (SPSS, version 22) for Microsoft windows. The data were conveyed as Mean and Standard Deviation (S.D.). A two-sided p-value < 0.05 was considered statistically significant.

Sex distribution in the study involves a total of 68(sixty eight) patients. In the study population 57.3% (n=39) were males and 42.7% (n=29) were females (Figure 1) with a minimum age of 29 years and maximum age of 76 years (Figure 2). Regional wall motion abnormality was seen in 4.4% (n=3) of individuals who belong to CKD stage4 in the study out of 68 patients (Table 1).

57 people(83.8%) had Diastolic Dysfunction of which 7.3% (n=5) had grade 1 diastolic dysfunction, 38.2% (n=26) had grade 2 diastolic dysfunction and 38.2% (n=26) had grade 3 diastolic dysfunction (Figure 3) with a p value of 0.18 (not significant). In this study, 44 people out of the 68 people had significant interventricular thickness. 64.7% (n=44) had inter ventricular thickness greater than 12 mm, whereas 35.3% (n=24) had less than 12 mm (Figure 4). The presence of interventricular wall thickness in all stages of CKD is statistically significant(p=0.046).

In this study, 83.8% (n= 57) had significant lowered ejection fraction of which 4.4% (n=3) belong to stage 3, 73.4% (n=50) belong to stage 4 and 7.35% (n=4) belong to stage 5 CKD (Figure 5). The mean ejection fraction of all the patients is 44.57 % $\pm$8.2%. 33.34% of CKD stage 3, 92.57% of CKD stage 4, 80% of CKD stage 5 had deranged ejection fraction which is statistically significant(p<0.01).

In the study population, 83.8% (n= 57) had abnormal E/A ratio of which 2.9% belong to stage 3 CKD, 73.5% belong to stage 4 CKD and 7.3% belong to stage 5 CKD (Figure 6). The mean E/A ratio was 0.61$\pm$0.11. 22.23% of CKD stage 3, 92.7% of CKD stage 4, 100% of CKD stage 5 had abnormal E/A ratio which is statistically significant(p<0.01). In the study population, 67.6 % (n=46) had abnormal fractional shortening of which 60.2% (n=41) had fractional shortening <0.25 and 7.3% (n=5) had > 0.45 (Figure 7). Fractional shortening is significantly reduced in the study population which is statistically significant (p<0.01).

CONCLUSION

Sixty-eight patients with Chronic Tubulo Interstitial Syndrome without any noticeable cardiac abnormalities were studied to identify echocardiographic defects. The following parameters were analysed to detect the cardiac abnormalities: Regional Wall Motion Abnormality (RWMA), Interventricular wall thickness (IVWT), Posterior ventricular wall thickness (PVWT), Ejection Fraction (E.F.), Fractional Shortening (F.S.), E/A ratio, Valvular lesions, Pericardial Effusion. Of the above parameters Inter ventricular wall thickness, Posterior ventricular wall thickness, Ejection Fraction, Fractional shortening and E/A ratio had significant association among the patients with asymptomatic CTIS.

From this study, it is concluded that patients with Chronic Tubulo Interstitial Syndrome in various stages of CKD have asymptomatic echocardiographic abnormalities. Further studies are needed in the future to determine whether interventions targeting these asymptomatic abnormalities have

any substantial effect on the morbidity and mortality in these patients.

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Conflict of Interest

No potential conflict of interest.

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