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Original Article

# Effect of diabetes mellitus on markers of left ventricular dysfunction in chronic kidney disease

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ABSTRACT

*Objectives:* To identify markers of left ventricular dysfunction in chronic kidney disease (CKD) and the effects of diabetes mellitus on them.
*Methods:* This was a cross sectional study of 200 consecutive chronic kidney disease patients (stage III-V). Echocardiographic assessment of left ventricular function including left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), left atrial volume, grade of diastolic dysfunction, E/E', left and right ventricular myocardial performance indices (LVMPI, RVMPI) were compared between diabetic and non-diabetic CKD.
*Results:* LVMI significantly increased with increasing stage of CKD ($p < 0.001$) in both diabetics (158.82 ± 48.76 gm/m$^2$ in stage III to 201.06 ± 63.62 gm/m$^2$ in stage V) and non-diabetics (133.14 ± 43.06 gm/m$^2$ stage III to 196.24 ± 58.75 gm/m$^2$ in stage V). This was significantly higher among diabetics of similar CKD stage compared to non-diabetics ($p = 0.001$). The LVEF worsened with increasing stage of CKD ($p = 0.002$) and was significantly reduced in diabetic patients (LVEF 61.96 ± 8.48 % in stage III CKD to 51.62 ± 13.45 % in stage V CKD) ($p < 0.001$). Diastolic dysfunction (Grades ≥2) and LA volume increased significantly with stage of CKD ($p < 0.001$) and was higher among diabetics ($p = 0.048$). Pulmonary artery systolic pressure (PASP) increased with increasing stage of CKD ($p < 0.001$), and was higher among diabetics ($p = 0.035$). E/E' worsened significantly with increasing stage of CKD and was also significantly higher in diabetics ($p < 0.001$). LVMPI ($p < 0.001$) and RVMPI ($p < 0.001$) were significantly reduced with worsening stage of CKD and in diabetics.
*Conclusion:* Advancing CKD stage was linearly associated with progressive left ventricular dysfunction which was significantly greater in diabetics.


## 1. Introduction

Less effort has been dedicated to evaluating the mechanisms related to myocardial dysfunction in CKD. Approximately 80 % of patients with end-stage CKD have left ventricular (LV) abnormalities (uraemic cardiomyopathy) on echocardiography.[2] Echocardiographic measures of left ventricular function which are independently associated with worse cardiovascular outcomes in CKD [13]include left atrial dimensions, left ventricular ejection fraction <55 % and LVMI.[18–20]

Cardiovascular risk in this population can partially be attributed to an increased association with traditional risk factors and risk factors of coexisting CKD.[1]

The major factors that contribute to furthering heart failure in diabetic nephropathy patients include cardiac microangiopathy, neuropathy of the cardiac autonomous nervous system, disturbed metabolism, and fatty degeneration of the myocardium.[1]

The aim of our study is to compare left ventricular systolic and diastolic function on echocardiography in patients in various stages of CKD and to identify markers of worsening LV function. We also

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aim to study the effect of diabetes on left ventricular function in patients with CKD.

## 2. Methods

We screened 315 patients of CKD of which 200 consecutive patients with CKD stages III to V were included. The protocol for this study was approved by our institutional review board, and all enrolled patients gave written informed consent.

Inclusion Criteria: All adult patients in stage III-V of CKD undergoing echocardiography were studied. Patients with evidence of kidney damage lasting for more than 3 months were classified into CKD stage III, IV or V based on estimated glomerular filtration rate (eGFR) level (mL/min/1.73m2) calculated by modified MDRD formula[23] of 30–59, 15 to 29, and <15, respectively.

Exclusion Criteria: Patients with normal renal function, children <18years, pregnant women, poor echo window, prior myocardial infarction-diagnosed by prior history or q waves on the ECG or having significant regional wall motion abnormalities, malignancies or patients on chemotherapeutic drugs that would affect or worsen left ventricular function, rheumatic valvular heart disease, cardiorenal syndromes type1 and 2, pre-existing dilated cardiomyopathy prior to onset of renal dysfunction, sepsis and other acute conditions that could worsen left ventricular function were excluded.

A detailed history and physical examination were done in all patients, fundus examination and a renal ultrasound for kidney size. Biochemical investigations were done at the NABL (National Accreditation Board for Laboratories) accredited laboratory of our college.

A patient was classified as diabetic nephropathy probably causing CKD if he had history of diabetes and abnormal fasting glucose along with mild to moderate proteinuria, fundus examination suggestive of diabetic retinopathy and almost normal sized kidneys. Diabetics with no proteinuria or nephrotic range proteinuria were excluded.[30] HBAIC was not used to diagnose diabetes because most of our patients were anaemic and the HBAIC values would be falsely low. In case of any discrepancy a consensus opinion of both nephrologist and endocrinologist was used.

### 2.1. Echocardiographic evaluation of cardiac structure and function

A detailed echocardiographic evaluation was done in each patient using VIVID3 echocardiography machine (GE Medical systems).

Two-dimensional, M mode, colour and tissue doppler images were recorded in the standard echocardiographic views. The echocardiographic measurements included left atrial diameter (LAD), left ventricular internal diameter in diastole (LVIDd), left ventricular internal diameter in systole (LVIDs), RV diameter, LV posterior wall thickness (LVPWd), and interventricular septum thickness (IVSd) in diastole.[10]

LV mass was measured using the Devereaux–modified cubed method using the formula recommended by the American Society of Echocardiography,[14,16] which was divided by body surface area (BSA) to obtain left ventricular mass index (LVMI).

Left ventricular hypertrophy (LVH) was defined when LVMI exceeded 115 g/m2 and 95 g/m2 for men and women respectively,[14] Left ventricular ejection fraction (LVEF) which was calculated in all patients using Simpson's method.[15] Systolic dysfunction was defined as LVEF <55 %.[15]

Left atrial volume was calculated using the prolate ellipse method,[15] which was divided by BSA to obtain left atrial volume index. Diastolic function was estimated by measuring the peak early transmitral filling velocity(*E*), and peak late transmitral filling velocity(*A*), calculating the *E/A* ratio, and measuring the deceleration time. These were then graded into the stages of diastolic dysfunction.[15]

Tissue doppler was done in all patients. E/E′ was calculated by dividing the transmitral E velocity by E′ obtained by tissue doppler. E′ was calculated by taking a mean of tissue doppler E′ velocities at the lateral annulus and medial annulus with a value of E/E' >15 considered as a poor prognostic sign.[12]

Colour Doppler imaging was done to see for mitral, tricuspid and aortic regurgitation which were then graded according to their severity.[15] PASP was estimated from TR jet by adding right atrial (RA) pressure to peak TR gradient.[22] The RA pressure was estimated by measuring the IVC size and distensibility.[15]

Myocardial performance index for ventricles was calculated using the formula MPI = (total systolic time - ejection time)/ejection time. Normal MPI is less than 0.40 and progressively greater values imply progressively worse ventricular function.[15] Right ventricular MPI >0.43 is suggestive of RV dysfunction.[14]

### 2.2. Statistical analysis

Descriptive statistics were reported using mean and standard deviation, number and percentages. The chi square test was done to assess the association between categorical variables. Independent *T* test was done to compare between the groups for all the outcome variables. Analysis of covariance (ANCOVA) was done to find the factors associated with the outcome variables, adjusting for age BMI, albumin. Logistic regression analysis was done to find the predictors for abnormal left ventricular ejection fraction and left ventricular diastolic dysfunction of grade $\geq$2 adjusting for age, BMI and albumin. Natural log value LVMI, LVEF and E/e' were computed and compared with the stage of CKD. Log values were used for some parameters as these were not normally distributed. Variables which were not normally distributed were log converted. The log converted values were then used for statistical analysis. A p value $< 0.05$ was considered significant. All the statistical analysis was done using SPSS version 17.

## 3. Results

Total number of patients studied was 200, of whom 138 patients (69 %) were male. The mean age of the study population was 55.65 ± 15.49 years. There were 50 patients (25 %) in CKD stage III, 60 (30 %) in CKD stage IV and 90 patients (45 %) in CKD stage V.

Diabetic nephropathy was the probable cause of chronic kidney disease in 100 (50 %) patients, hypertension causing CKD in 37 (18.5 %), chronic glomerulonephritis (CGN) 12 (6 %), unknown causes 19 (9.5 %), chronic interstitial nephritis 4 (2 %), obstructive uropathy 8 (4 %), autosomal dominant polycystic kidney disease in 3 (1.5 %), multiple myeloma 2 (1 %), SLE 3 (1.5 %). Other causes like Ig A nephropathy, primary amyloidosis, polyarteritis nodosa, vesicoureteric reflux, multisystem connective tissue disorders, genitourinary TB were less than 1 %.

The baseline characteristics among the diabetic and non-diabetic groups of CKDs were almost similar except for age and body mass Index (BMI) which were significantly lower in the non-diabetic group. When clinical signs were compared, fatigue was significantly higher in the diabetics with a significantly higher incidence of heart failure.

The use of beta blockers, statins and aspirin was significantly higher in the diabetic group whereas use of calcium channel blockers was significantly higher in the non-diabetic group. Serum albumin was significantly lower in the diabetic population. There was no significant difference in the baseline haemoglobin, serum

**Table 1**
**Baseline characteristics of CKD population.**

| Characteristic | Diabetic CKD n = 100 | Nondiabetic CKD n = 100 | p Value |
|---|---|---|---|
| Age(yrs) | 60.07 ± 11.86 | 51.13 ± 17.27 | <o.oo1 |
| Sex(males%) | 64 | 72 | 0.409 |
| BMI kg/m2 | 24.70 ± 4.59 | 23.03 ± 4.19 | 0.008 |
| GFR ml/min | 19.82 ± 13.46 | 21.61 ± 16.94 | 0.475 |
| Disrtibution among stages(n) | Stage iii-23 iv-32v-45 | STAGE iii-27 iv-28v-45 | 0.72 |
| Hemodialysis (%) | 32 | 29 | 0.3 |
| Prior cad (%) | 7 | 3 | 0.16 |
| Prior heart failure(%) | 7 | 1 | 0.032 |
| Prior CVA(%) | 5 | 4 | 0.50 |
| Smoking(%) | 22 | 26 | 0.31 |
| Alcohol intake(%) | 12 | 10 | 0.41 |
| Systolic blood pressure mmhg | 138.76 ± 24.43 | 141.6 ± 28.07 | 0.446 |
| Anemia(%) | 78 | 71 | 0.165 |
| ACE inhibitors(%) | 20 | 7 | 0.06 |
| Beta blockers(%) | 31 | 18 | 0.022 |
| Calcium channel blockers(%) | 41 | 57 | 0.017 |
| Aspirin(%) | 21 | 4 | < 0.01 |
| Statin(%) | 17 | 6 | 0.013 |
| Use of ≥ 2 antihypertensive(%) | 70 | 62 | 0.08 |
| Dyspnea(%) | 54 | 48 | 0.24 |
| Chest pain(%) | 9 | 12 | 0.32 |
| Fatigue(%) | 42 | 29 | 0.038 |
| Palpitations/syncope(%) | 3 | 2 | 0.249 |
| Raised JVP(%) | 13 | 8 | 0.17 |
| Pedal edema(%) | 29 | 14 | 0.06 |
| LVS3(%) | 8 | 0 | 0.003 |
| RS-basal creps(%) | 13 | 2 | 0.003 |
| HB mgldl | 9.55 ± 1.79 | 9.79 ± 2.86 | 0.475 |
| SR albumin gm/dl | 2.90 ± 0.69 | 3.16 ± 0.76 | 0.013 |
| SR calcium mg/dl | 8.11 ± 0.74 | 8.29 0 ± 0.86 | 0.12 |
| Serum phosphorous mg/dl | 4.63 ± 1.39 | 4.92 ± 1.49 | 0.158 |

calcium, serum phosphorous and uric acid between the two groups (Table 1).

Echocardiographic parameters in the CKD population: The M mode demonstrated a significantly higher LVIDd and LVIDs in diabetics with CKD. The left ventricular ejection fraction was also significantly lower. The left ventricular mass index although higher among the diabetic population was not statistically significant. The incidence of diastolic dysfunction of grades ≥2 and of mitral regurgitation of grade 2 or more was higher in the diabetic versus the non-diabetic subgroups. The incidence of moderate to severe TR however did not vary between the two. The pulmonary artery systolic pressures were also significantly higher in the diabetic population (Table 2).

When we analysed the effect of the stage of CKD and diabetes on echocardiographic parameters, more advanced stages of CKD had worsening of all echocardiographic parameters. Severe LV

**Table 2**
**Echocardiographic Parameters based on the stages of CKD- diabetic versus nondiabetic population.**

| Parameter | Diabetic CKD (n = 100) | | | Nondiabetic CKD(n = = 100) | | | P value |
|---|---|---|---|---|---|---|---|
| STAGES | III | IV | V | III | IV | V | |
| LA volume ml | 33.31± | 42.32± | 47.13± | 27.73± | 33.25± | 48.59± | <0.001[a] |
| | 14.07 | 12.83 | 16.07 | 10.07 | 15.24 | 18.21 | 0.048[b] |
| LVMI gm/m2 | 158.82 ± 48.76 | 171.24± | 201.06± | 133.14± | 158.90± | 196.24± | <0.001[a] |
| | | 46.36 | 63.62 | 43.06 | | 58.75 | 0.034[b] |
| LAVI(LA volume index ML/M2 BSA) | 20.29± | 24.63± | 28.66± | 17.03± | 20.81± | 23.8± | <0.001[a] |
| | 24.63 | 6.26 | 10.10 | | 9.77 | 11.35 | 0.15[b] |
| LVEF % | 61.96± | 58.84± | 51.62± | 65.85± | 66.04± | 64.60± | 0.002[a] |
| | 8.48 | 11.69 | 13.45 | 7.67 | 8.03 | 6.14 | <0.001[b] |
| LVDD Grade≥2 | 8 (34.8) | 26 (81.3) | 36 (80.0) | 6 (22.2) | 12 (42.9) | 34 (75.6) | <0.001[a] |
| | | | | | | | 0.009[b] |
| PASP mmHg | 35.13± | 41.59± | 47.69± | 31.11± | 37.07± | 44.58± | <0.001[a] |
| | 10.4 | 15.32 | 13.07 | 5.47 | 11.47 | 18.01 | 0.035[b] |
| E/E′ | 10.74± | 15.37± | 15.82± | 7.81± | 10.58± | 13.14± | <0.001[a] |
| | 5.38 | 6.40 | 6.09 | 3.4 | 4.76 | 5.41 | <0.001[b] |
| LVMPI | 0.25± | 0.27± | 0.38± | 0.25± | 0.23± | 0.28± | 0.010[a] |
| | 0.09 | 0.15 | 0.27 | 0.14 | 0.09 | 0.14 | 0.087[b] |
| RVMPI | 0.31± | 0.32± | 0.34± | 0.24± | 0.24± | 0.25± | 0.65[a] |
| | 0.17 | 0.18 | 0.18 | 0.08 | 0.08 | 0.11 | 0.001[b] |

All values are mean ± standard deviation.
Ancova analysis to adjust for age and BMI done for all parameters.
LVMI- Left ventricular mass Index, LVMPI- Left ventricular Myocardial performance Index, RVMPI- Right Ventricular Myocardial Performance Index.
[a] *P* value for stage of CKD.
[b] p value for DM CKD vs NON DM.

dysfunction was seen more in diabetics as well as greater worsening of echocardiographic parameters (Table 2). The LA volume and LV mass index were significantly higher with worsening stage of CKD and in diabetics (Fig. 1). The left ventricular ejection fraction significantly decreased as the stage of CKD increased. However, this worsening of LV systolic function was much more pronounced in the diabetics with a statistically significant interaction effect. The LVEF did not change significantly among non-diabetics (Fig. 2). The p value for effect of stage of CKD was 0.002. This implies that overall although the left ventricular ejection fraction worsened as the stage of CKD worsened most of the worsening was due to the worsening of LVEF in the diabetic population, with not much worsening seen among the non-diabetics with similar stage of CKD.

The left ventricular diastolic dysfunction worsened significantly with advancing stage of CKD. The number of patients with Left ventricular diastolic dysfunction of grade ≥2 increased from 8 (34.8 %) in stage III to 36 (80 %) in stage V among diabetics and from 6 (22.2 %) in stage III to 34 (75.6 %) in stage V among non-diabetics ($p < 0.001$ for effect of CKD stage on LVDD and $p = 0.009$ for effect of DM on LVDD).

The E/E′ worsened significantly with stage of CKD and was significantly worse in the diabetic population. E/E′ increased from 10.79 ± 5.38in stage III to 15.82 ± 6.09 in stage V in diabetics. Among non-diabetics it increased from 7.81 ± 3.4 in stage III to 13.14 ± 5.41 in stage V. The p value on ANCOVA for effect of CKD stage on E/E' was <0.001 and for effect of DM was <0.001 (Fig. 3).

The left ventricular myocardial performance index (LVMPI) worsened with advancing stage of CKD and was also worse among the diabetics. The p value for effect of CKD stage on LVMPI was 0.010 and for effect of DM was 0.087. When we assessed RVMPI (right ventricular myocardial performance index) we found that the p value for effect of DM was 0.0001 but for effect of CKD stage was 0.65. The RVMPI did not worsen significantly with increasing CKD stage but was significantly worse in diabetics compared to nondiabetics.

On statistical analysis using ANCOVA analysis of covariance for significant predictors of left ventricular systolic dysfunction defined as left ventricular ejection fraction <55 %,[15] we found worsening stage of CKD ($p = 0.004$), diabetes ($p < 0.001$), and serum albumin ($p = 0.03$) were significant predictors.

We further found that stage of CKD ($p < 0.001$), age ($p = 0.044$), and diabetes ($p = 0.09$) were significant predictors of LV diastolic dysfunction.

## 4. Discussion

In our study we found that advancing stage of CKD was linearly associated with progressive left ventricular systolic and diastolic dysfunction. Diabetics with CKD had a significant increase in left ventricular mass index and left atrial volume, and of worsening in left ventricular ejection fraction, diastolic dysfunction, pulmonary hypertension, mitral regurgitation and myocardial performance indices of both ventricles.

Szu Chia Chen et al,[1] while comparing LVMI and LVEF in diabetic patients in stages 3–5 of CKD also found that increases in LVMI and decreases in LVEF coincided with advances in CKD stages in diabetic patients.

Several authors have found a linear relationship of advancing stages of CKD with worsening of LVMI [6,9]and diastolic function[5], independent of other influencing factors such as age, blood pressure, renal function, anaemia[4,11]and LV hypertrophy.[3,8,21]

Hypoalbuminemia has been correlated with altered left ventricular structure and function and LV systolic dysfunction.[26,27,28,29] Szu Chia Chen et al[1] found an inverse relationship between serum albumin levels and LVMI which is consistent with our study.

Angela Y et al[12] studied left ventricular filling pressures by Doppler in patients with end-stage renal disease and found that E/E' ratio displayed important additional prognostic information above and beyond LV mass and systolic function. Elektra et al[7] found that myocardial performance index is independent of acute load changes and is a better indicator of global left ventricular function in the presence of volume shifts as occurs in CKD patients on dialysis. We found that LVMPI worsened with advancing stages of CKD but there was no significant worsening in RVMPI.

The importance of screening CKD patients for LV dysfunction on echocardiography may help identify markers of LV dysfunction which can impact prognosis in these patients.[24,25] Although ours is a cross-sectional study, we have identified echocardiographic markers of LV systolic and diastolic dysfunction with worsening stage of CKD and that these markers were more pronounced in

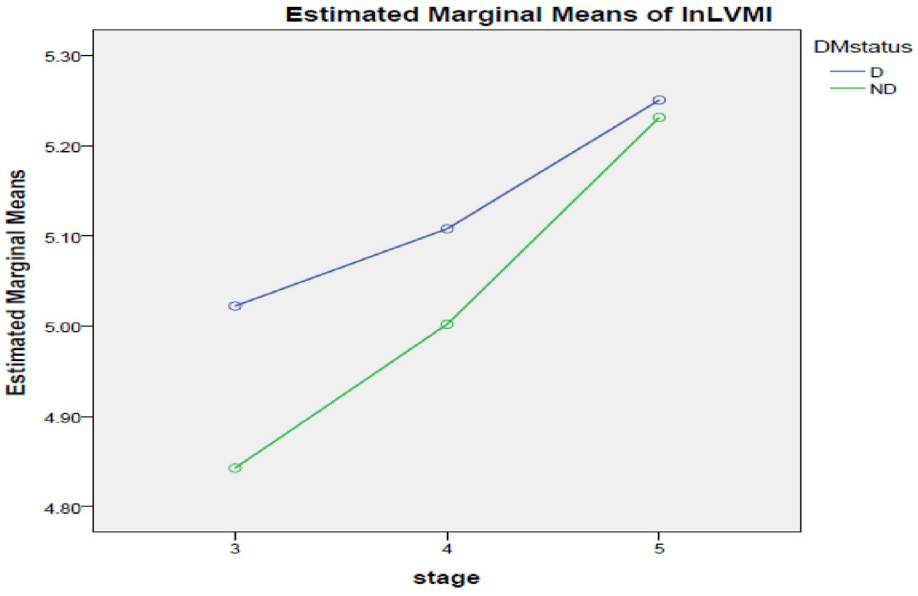


**Fig. 1.** Left Ventricular Mass Index in CKD.

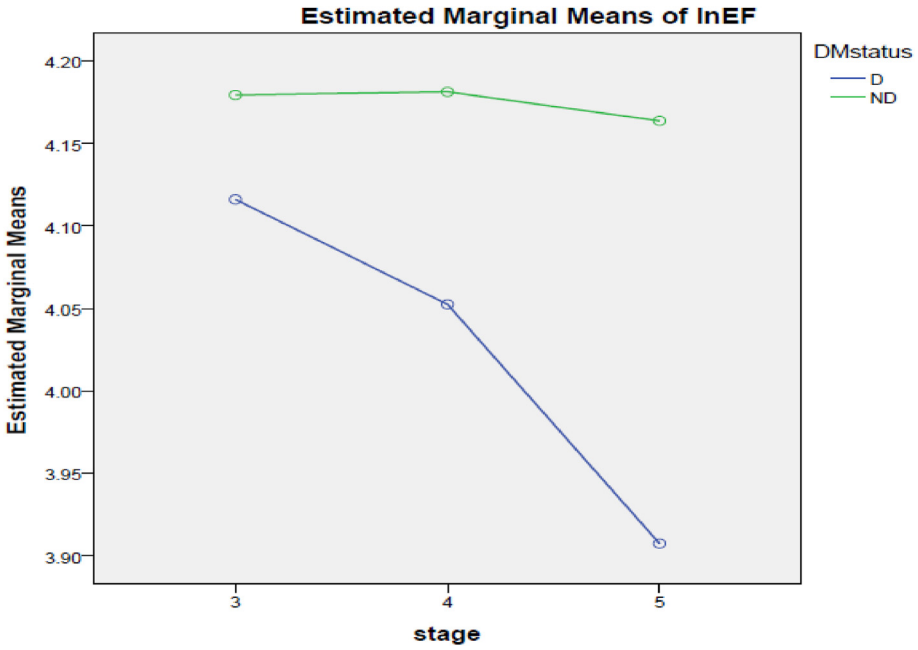


**Fig. 2.** Left ventricular ejection fraction in CKD.

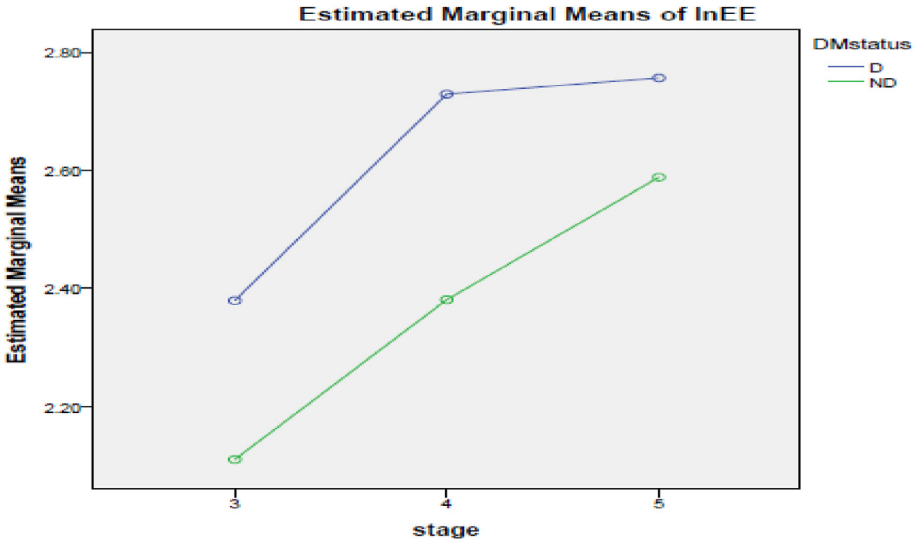


**Fig. 3.** E/E′ in CKD (Diastolic Dysfunction Index).

diabetics across all stages of CKD. This is the first study to our knowledge that studies extensively all echocardiographic parameters in CKD population with a correlation with stages of CKD.

### *4.1. Limitations of the study*

The study was carried out in a tertiary referral centre and hence might be subject to referral bias reflecting a more morbid population.

Our study had a cross-sectional design, and thus the predictors of cardiovascular events could not be evaluated. Prospective studies in larger samples may be needed to discern correlation of these markers with clinical outcomes. We could not do a 3D echo evaluation or strain imaging due to logistic constraints which would have greatly improved the echocardiographic assessment of ventricular mass and LA volume and LVEF.

## 5. Conclusions

Advancing stage of CKD was linearly associated with progressive left ventricular dysfunction. Diabetics with CKD had a significant increase in left ventricular mass index, left atrial volume, reduced left ventricular ejection fraction, advanced LV diastolic dysfunction, pulmonary hypertension, mitral regurgitation and worse myocardial performance indices of both ventricles. The stage of CKD, diabetes, low serum albumin were predictors of LV systolic dysfunction, while advanced age, diabetes and advancing stage of CKD were predictors of LV diastolic dysfunction.

What is already Known.

1. Progression of chronic kidney disease is associated with worsening left ventricular diastolic dysfunction and increase in left ventricular mass index

What the study adds.

1. Advancing stage of CKD was linearly associated with progressive left ventricular dysfunction, worsening mitral regurgitation, pulmonary hypertension and myocardial performance indices of both ventricles.
2. The worsening in left ventricular ejection fraction and diastolic dysfunction with worsening stage of CKD is much more significant in diabetics.
3. This is the most comprehensive echocardiography study till date in the chronic kidney disease population with extensive evaluation of all echocardiographic parameters.
4. The stage of CKD, diabetes, low serum albumin were predictors of LV systolic dysfunction,
5. Advanced age, diabetes and advancing stage of CKD were predictors of LV diastolic dysfunction

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