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# Deciphering the Role of Vitamin D on Cardiac Physiology in Patient with Predialysis Diabetic and Non-Diabetic Chronic Kidney Diseases: An Observational Report

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## ABSTRACT

**Background:** Chronic kidney disease (CKD) represents a significant global health issue, closely associated with cardiovascular complications. A notable prevalence of vitamin D deficiency exists among individuals with CKD, which may play a role in cardiovascular dysfunction; however, the precise nature of this relationship is not fully understood.

**Objective:** This study evaluates the effects of vitamin D deficiency on cardiovascular parameters in patients with CKD comparing those with diabetes to those without, in the eastern India.

**Methods:** A cross-sectional study was performed on individuals diagnosed with CKD to assess their levels of vitamin D, left ventricular mass index (LVMI), and ejection fraction (EF). Participants were divided based on their diabetic status and the stage of CKD. Statistical analyses were executed to identify potential associations between vitamin D deficiency and cardiovascular parameters.

**Results:** Diabetic patients with CKD exhibited a more severe deficiency of vitamin D than their non-diabetic counterparts. A significant link was established between low vitamin D concentrations and an increase in left ventricular mass index (LVMI), which may indicate a relationship with cardiac remodelling. However, no significant correlation was found between vitamin D levels and ejection fraction, implying that other variables may play a role in cardiac dysfunction associated with CKD.

**Conclusion:** Our findings indicate a pressing requirement for the early recognition and management of vitamin D deficiency in individuals with CKD, especially in diabetic patients, to alleviate cardiovascular risks. Further research is essential to investigate targeted therapeutic interventions.

***Keywords:*** Chronic kidney disease, cardiovascular dysfunction, diabetic patients, vitamin D,

## INTRODUCTION

Chronic kidney disease (CKD) is an emerging public health concern worldwide (1,2) and one of the strongest indicators of premature cardiovascular complications (3). CKD encompasses different pathophysiologic phenomenon associated with abnormal kidney function and persistent decline in glomerular rate (GFR) (4). Though cardiovascular impairments are prevalent in individuals with chronic kidney disease (CKD), conventional risk variables are insufficient to explain those occurrences (5). Cardiovascular diseases; characterized by the appearance of congestive heart failure (CHF), ischemic heart disease (IHD) or left ventricular hypertrophy (LVH) are prevalent in cohorts with established CKD (6). Before their kidney failure necessitates replacement therapy, majority CKD patients without even exhibiting uremia pass away due to severe cardiovascular complications (7). Recent studies suggest that, the frequency of LVH of patients with early stages of renal impairment is greater than the general population and the risk of LVH improves with progressively declining renal function (8).

Deficiency of vitamin D as a non-traditional risk factor is extremely prevalent in chronic kidney disease (CKD) (9) due to the lack of its precursor (25 hydroxyvitamin D3) and impaired activity of the kidney enzyme 1α-hydroxylase which converts this precursor to the active hormone (10). Recent studies suggest that importance of vitamin D can be extended beyond its canonical function to preserve the calcium and phosphate equilibrium (11). As a cell-differentiating and anti-proliferative agent, vitamin D has been reported to be a crucial player in the immune (12,13), cardiovascular (14), and renal systems (15,16) homeostasis controlling lipid metabolism (17,18), inflammation (19), cellular proliferation (20), differentiation (20) through its interaction with intracellular vitamin D receptor (VDR). Both the classical and non-classical effects of vitamin D appear to focus on the kidney (21, 22) and cardiac tissues (23,24) where the expression of VDR has been reported. Though, administration of calcitriol to experimental animals or patients has been shown to improve cardiac function through meta-analyses (25-27), small clinical trials and observational studies; still there is insufficient convincing evidence to support the claim that vitamin D treatment enhances cardiovascular health.

Observational studies have demonstrated association between vitamin D insufficiency and elevated risk of cardiovascular events in CKD patients (28, 29). The traditional risk factors for cardiovascular disease such as hypertension, dyslipidaemia, diabetes and obesity have been reported to overlap with the clinical manifestations of the CKD populations (30). Whereas diabetes mellitus has been also considered as one of the major contributors for CKD related morbidity (31). It is also observed that diabetic individuals have a higher probability of having a severe 25(OH)-vitamin D deficiency (< 10 ng/mL) compared to the non-diabetic ones (22% vs. 17%) (32,33). In spite of having these reports there is few studies in India regarding cardiovascular outcome in vitamin D deficient CKD patients. Hence, this study was designed to delineate effects of vitamin D deficiency in diabetic and non-diabetic CKD population from Eastern India.

### Aims and Objectives:

The investigation of the association between vitamin D levels and cardiac physiology in predialysis diabetic and non-diabetic chronic kidney disease (CKD) patients.

## MATERIALS & METHODS

**Study area:** Both rural and urban catchment area of NRS Medical College and Hospital, Kolkata.

**Study Population:** Patients of CKD attending the Out Patients Department

(OPD) and subsequently admitted in indoor department of general medicine of NRS Medical College and Hospital, Kolkata.

**Plan for data analysis-** The case records were studied, analysed and compared with suitable statistical method. Correlations between different findings were established by bar diagrams, pie charts wherever feasible.

**Inclusion criterion:** Age 18-75, CKD patients not requiring dialysis (eGFR<60 ml/min), any level of vitamin D

**Exclusion criterion:** History of heart failure or gross fluid overload, History of myocardial infraction, cerebrovascular accident, active infection, active autoimmune disease, malignancy.

**Study period:** December; 2011 to July; 2013.

**Sample size:** Fifty (50) patients

**Sample design:** Simple random selection

**Study design:** Prospective Observational Study, with proper consent of the patients after explaining the nature of the study.

**Study tools:**

a) Demographic parameter: Name, Age, Sex, Family History, Education, Economic status,
b) Clinical parameter: Weight in Kg, Height in meter, BMI, BP. smoking history relevant clinical examination of all system.
c) Biochemical parameter: Vit D level was assessed by electrochemiluminescence immunoassay. Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), Urea, creatinine, sodium, potassium, calcium, phosphate, serum uric acid
d) Cardiological parameter:

**1. ECG in all leads**

**2. *Echocardiography:*** Left Ventricular dimensions, inter ventricular septal thickness (IVST), left ventricular mass. Measures of systolic function by ejection fraction. Measures of diastolic function according to grading.

e) Others:

1. Haematological: Hb, TC, DC, ESR, PLATELET, MCV, MCH, MCHC,
2. Urine: for R/E &M/E, C/S
3. USG of KUB
4. Chest X-ray
5. Lipid profile
6. ANA (where applicable)

**Methods**

All the participants of the investigation had been hospitalized to the internal medicine department or selected at random from the nephrology and medicine OPD. They were all not on vitamin D supplements and had not yet begun dialysis. Each of them underwent a comprehensive clinical assessment, which was followed by pertinent laboratory investigations. Individuals who were on insulin, oral hypoglycaemic medications, diagnosed with diet-controlled diabetes or whose fasting blood sugar was 126 mg/dL or above were classified as diabetics. The KDOQI guidelines were followed for the diagnosis of chronic kidney disease and eGFR was employed for staging. Estimation of Vitamin D levels were done.

**Details of some investigation procedures:**

- **Echocardiography** of the selected patients were performed (using M mode) to see the following measurement*:(i) Size of left ventricle in systole and diastole. (ii) Left Ventricular Internal Diameter (LVID) in diastole. (iii) Posterior Wall Thickness (PWT) at the end of diastole. (iv) Final diastolic and systolic volume. (v) Ejection fraction for systolic function. (vi) Inter-ventricular septal thickness s(IVST). (vii)Diastolic dysfunction assessment.*
- **Method for estimation of blood urea:** For quantitative estimation of urea nitrogen in serum *Di-acetyl monoxime method* was utilized in which Urea reacts with diacetyl monoxime in hot acid medium producing some pink

colour complex. The intensity of the complex is measured colorimetrically at 520 nm (range 510- 540) which is proportional to the concentration of urea nitrogen in the specimen under test.

- **Method for estimation of serum creatinine:** It is quantified with *Alkaline picrate method* in which Creatinine reacts with alkaline picrate and produces a red coloured complex. The intensity of the complex is measured colorimetrically. Normal range: 0.9 – 1.5 mg/dl.
- **Estimated Glomerular Filtration Rate (eGFR):** MDRD formula had been employed using android application. The formula utilized was *eGFR (ml/min per 1.73 $m^2$) =186.3×$(P_{Cr})^{-1.154}$×$(age)^{-0.203}$× [1.212 if Black] × [0.742if Female]*
- **Method for estimation of serum sodium ($Na^+$) and potassium($K^+$):** To quantify *auto analyser (stat profile*) was utilized. Where normal value of $Na^+$: 136 – 145 mEq/ml and normal value of $K^+$:3.5 – 5 mEq/ml
- **Complete Haemogram including platelet count:** *Complete haemato autoanalyser* and reports were reviewed under microscopic examination. Normal value of male haemoglobin in male is 13mg/dl or above and that for female is 12 gm/dl and above. Normal platelet count ranges from 1.5 to 4 lacs/cumm. Normal leucocyte count ranges from 4000 to 11000 per cumm of blood.
- For estimating Bilirubin, Serum protein and serum albumin *Doumas reference method, TP method (Henry's modification of Kingsley's biuret method, Bromocresolgreen (BCG) method* were utilized respectively

## STATISTICAL ANALYSIS

Appropriate parametric and non-parametric statistical tests were performed to check any significant difference, correlation and association of parameters with the disease state. Results were plotted by bar diagram, pi charts, percentage where feasible. Chi-Square test was used to analyse non-parametric data and calculation of 'p' value. Multiple regression analysis was carried out using *back ward selection method*, regression criteria being p=>0.05 with vitamin D, eGFR, ejection fraction and haemoglobin as predictor with LVMI as regressor.

## RESULT

It is evident from figure:1A that majority of patients were males (62%) and the M:F ratio was found to be 1.63:1. It was observed (Fig:1B) that only 24% patients were from the age group 20-40 years, 58% were from 41-60years and 18% were more than 60 years old. Prevalence of diabetic CKD was observed more (46%) in age group 41 to 60 years while non–diabetic CKD was found at higher number in lower age group of 20-40 years (22%) (Fig: 1C).

Higher representation of diabetic CKD patients at earlier stage (III) (28%) was noted in comparison to non –diabetic CKD which tends to present mostly in later stages (V) (Figure: 2.A). It was also observed that (Fig: 2B), total 56% of all CKD patients were within 41 to 60 years of age group. Earlier stage (stage-iii) CKD was found in lower number for 20–40-year cohort compared to the cohorts with elder ages.

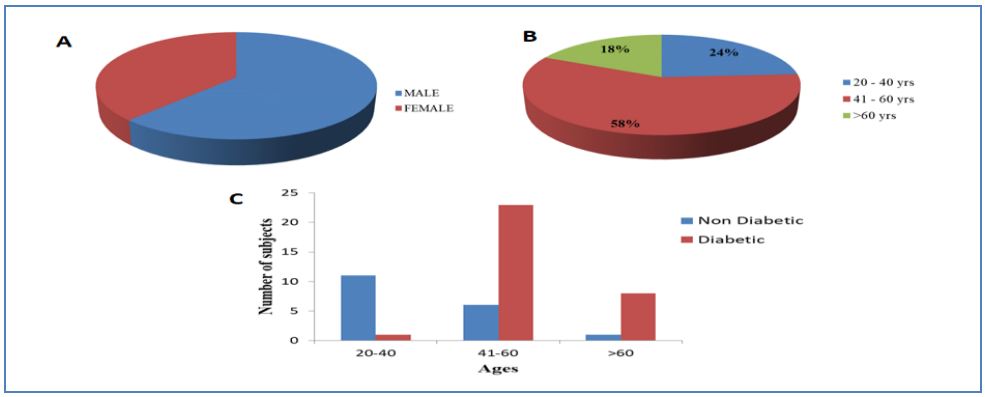


**Fig: 1: Age (1.B, 1.C) and gender (1.A) distribution of CKD patients**

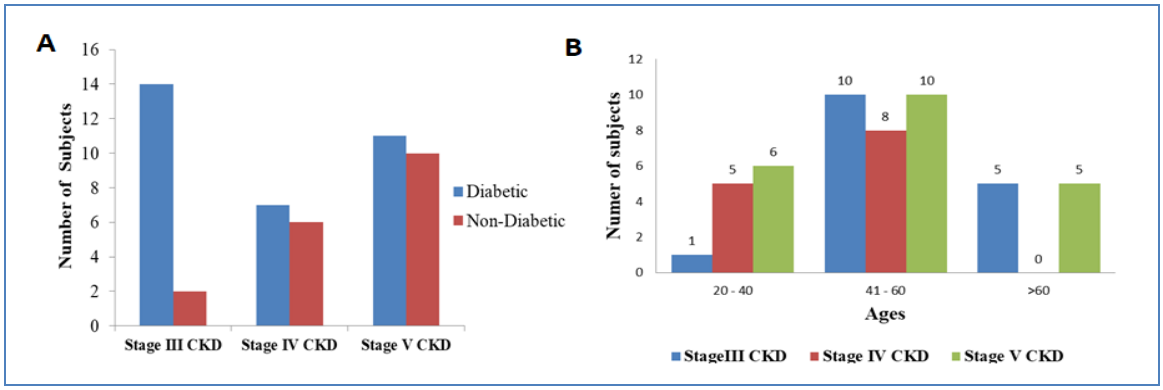


**Fig: 2.A: Stage wise distribution of diabetic and non-diabetic CKD patients; Fig:2B: Age wise arrangement of CKD patients with different grades**

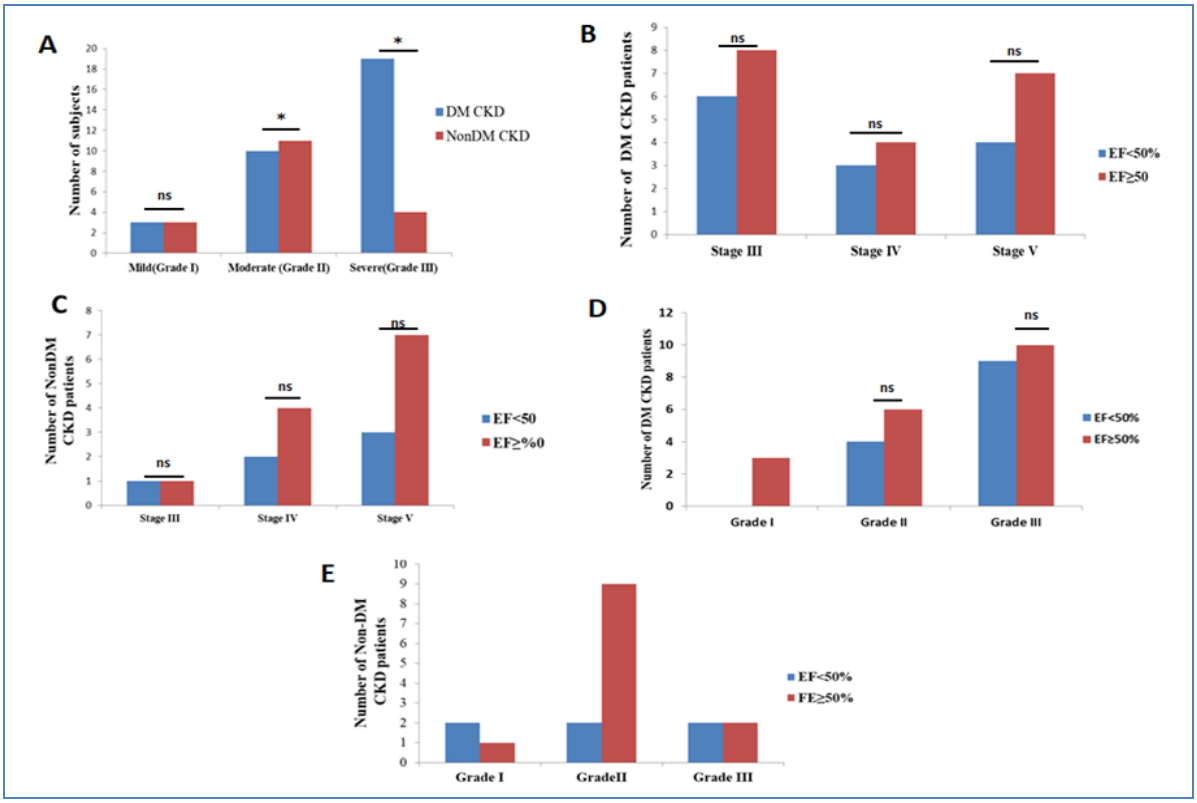


**Fig: 3A:** Relation between DM-CKD and Non-DM-CKD patients with Vitamin D deficiency level, Fig:3B: Association between ejection fraction and different DM-CKD stages; Fig:3.C: Association between ejection fraction and CKD stages of non-DM-CKD patients, Fig:3. D, E: Association between the ejection fraction and the grade of Vitamin D deficiency in both diabetic and non-diabetic CKD patients

Figure 3.A depicts diabetic CKD patients were significantly more deficient in vitamin D compared to the non-diabetic CKD ones. Non-significant correlation between ejection fraction and different stages of CKD was observed (Fig3.B) and we can infer that EF is not related to stages of DM-CKD patients. Even for the non-diabetic ones no significant association was found (Fig: 3.C) between the ejection fraction and different stages of CKD. Non-significant association was observed between the ejection fraction and the grade of Vitamin D deficiency in both diabetic (Fig: 3.D) and non-diabetic CKD patients (Fig: 3.E).

No statistically significant association (p=0.1) was found between vitamin D deficiency and diastolic dysfunction in diabetic CKD (Figure 4.A). Fig: 4.B showed, among (p=0.07) the stage V CKD 14% are grade II and 28% are grade III vitamin D deficient. This comparative association study is statistically significant to some extent (Fig: 4.B). Left ventricular Mass Index (LVMI) of each CKD patients were assessed as described in methodology. LVMI is classified as normal, mild, moderately and severely abnormal. Here, group I is referred as mildly abnormal, group II as moderately abnormal and group III as severely abnormal LVM. Highly significant correlation was found between different stages of vitamin D deficiency and different group of LVMI (p=0.0163) (Fig: 4.c).

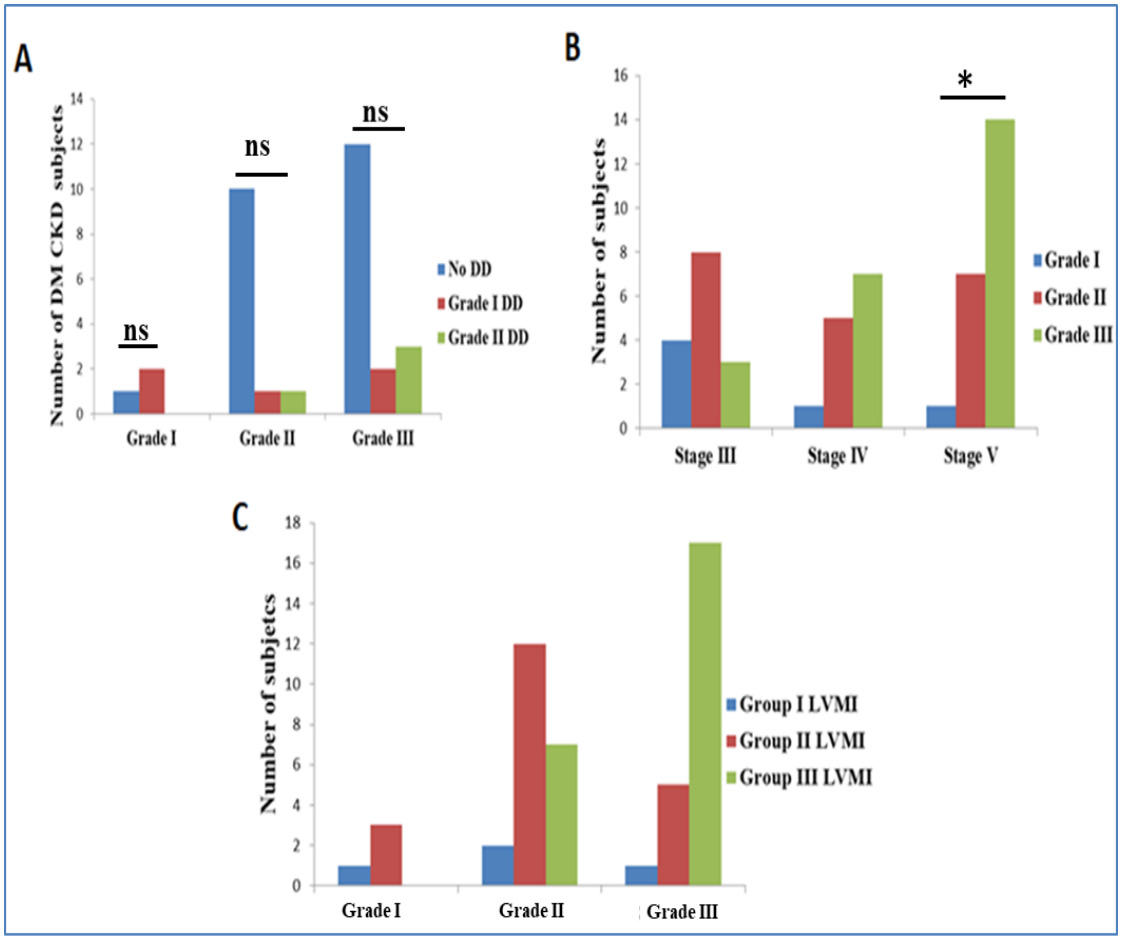


**Fig: 4A: The interrelation between different grades of vit. D deficiency and DM-CKD patients, Fig: 4B: Association between CKD grades and vit. D deficiency; Fig: 4.C: Relation between vit. D deficiency grades and LVMI groups of CKD patients**

Significant inverse correlation was observed (Table:1) between eGFR and LVMI. Significant correlation was observed (table: 1) between eGFR and vitamin D level. No

significant correlation was found between haemoglobin level and LVMI.

**Table :1**

| Correlations | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Age | eGFR | LVMI | VitD | EF | Hb |
| LVMI | *Pearson Correlation* | .119 | -.327* | 1 | -.356* | .173 | -.110 |
| | *Sig. (2-tailed)* | .409 | .021 | | .011 | .231 | .447 |
| | *N* | 50 | 50 | 50 | 50 | 50 | 50 |
| VitD | *Pearson Correlation* | -.234 | .357* | -.356* | 1 | .091 | .067 |
| | *Sig. (2-tailed)* | .101 | .011 | .011 | | .532 | .645 |
| | *N* | 50 | 50 | 50 | 50 | 50 | 50 |
| EF | *Pearson Correlation* | .167 | -.084 | .173 | .091 | 1 | -.018 |
| | *Sig. (2-tailed)* | .246 | .561 | .231 | .532 | | .899 |
| | *N* | 50 | 50 | 50 | 50 | 50 | 50 |
| Hb | *Pearson Correlation* | .186 | .362** | -.110 | .067 | -.018 | 1 |
| | *Sig. (2-tailed)* | .195 | .010 | .447 | .645 | .899 | |
| | *N* | 50 | 50 | 50 | 50 | 50 | 50 |
| *. Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2tailed) | | | | | | | |

**Table:1 shows correlation between different parameters affecting LVMI and Vitamin D status**

## DISCUSSION

According to our analysis, of the 50 patients, 31 (62%) were men and 19 (38%) were women. This result is consistent with standard literature observations indicating chronic kidney disease is more prevalent among male compared to females. This prevalence rate is comparable to research conducted by Singh et al. in India, where the MDRD formula was applied and 61% of the male and 39% of female subjects had all five stages of CKD (34).

In the current study, 24% of patients were between the ages of 20 and 40 years, 58% were within of 41 and 60 years, and 18% were older than 60 years. MM Rajapurkar et al., showed that the M:F ratio was 70:30 and the mean age was 50.1±14.6 years. Individuals from the East Zone were older, whereas those from the North Zone were younger (35). As to the 2010 CDC National Chronic Kidney Disease Fact Sheet, 4% of adults aged 20 to 44 had chronic kidney disease (CKD). 65 years of age or older to 90 years of age were 43% (36). In the present study; among 50 patients of CKD, 32(64%) were diabetic CKD and 18(36%) were found as non-diabetic CKD. Diabetic CKD has been found to be more prevalent in age group 41 to 60 years compare to younger ones with only 22% incidence of non-diabetic CKD .These finding corroborate with a study by V. Viswanathan et al; in which majority of diabetic CKD were observed within 40 to 65 years of age (37).It is evident from study by C P Wen et al. that, at the time of diagnosis, diabetic CKD presented more earlier stage that is stage I to IV (38). In our study among 64% of total diabetic CKD patients 48% present in stage III & IV compared to total 16% stage III & IV in non-diabetic CKD.

Levin et al. found that diabetic CKD affected 48% of the 1814 patients (39). Similar to our findings, research conducted in recent reports suggest that diabetic nephropathy accounts for 60.0% CKD (40). Additionally, the present investigation found that the occurrence of diabetes [p = 0.035] and female gender [p = 0.009] were independent predictors of 25(OH) D

insufficiency. In the current study, we additionally found that, in comparison to CKD patients without diabetes, those with diabetic CKD had considerably greater levels of vitamin D deficiency. Comparative to our findings, C A Usluogullari et al. reported that individuals with diabetes had a higher probability of having a severe 25(OH)-vitamin D deficiency (< 20 ng/mL) compared to those without the disease (70.8% vs. 38.8%) (41). Relation between stages of CKD and different grades of CKD were statistically significant to some extent (p=0.07). Our investigation showed that among stage V CKD 14% are grade II and 28% are grade III vitamin D deficient. Some previous reports from small clinic-based samples by Choovichian et al showed that there is significant association between vitamin D status and stages of CKD (42). In another study at Thailand by B Satirapo et al found that 25 hydroxyvitamin D levels were significantly lower according to severity of renal impairment (43). According to W Kosmala.et al., LV dysfunction is extremely prevalent in CKD patients and may be associated with mortality as well as the eventual development of heart failure (44). Diastolic dysfunction deteriorates parallel with the progression of LVH. According to J Miyazato. et al., diabetic nephropathy causes LV diastolic dysfunction, which particularly and significantly progresses in patients with CKD, regardless of LV hypertrophy (45). In our investigation; these results are not statistically significant. No significant association was observed between CKD patients' diastolic dysfunction and their vitamin D levels. Pilz S et al, found that there was a non-significant tendency toward an increased risk of diastolic dysfunction but no significant correlation between LV mass, LV systolic function, and serum levels of 25 (OH)D (46). In the current study, ejection fraction (EF) was found to be lower than 50% in 13 (40.6%) diabetic CKD patients and 33.33% of non-diabetic CKD patients (n = 18). EF was not found to be significantly correlated with CKD stage (p=0.8, p=0.9). Vitamin D insufficiency is not the only cause of the EF<50% seen in this study; there are other factors that might contribute to reduced left ventricular systolic function in individuals with chronic kidney disease.

The current investigation found a significant association between various vitamin D insufficiency stages and various aberrant LVMI groups in individuals with chronic kidney disease. Findings indicate that among CKD patients who are severely vitamin D deficient (stage III), 17 (35.4%) have severely abnormal (group III) LVMI, 5 (10.4%) have moderately abnormal LVMI, and 112 (25%) have group II LVMI and 7 (14.58%) have group III LVMI among moderately vitamin D deficient (stage II) patients.

## CONCLUSION

This investigation reveals a high prevalence of diabetic chronic kidney disease (CKD) among patients, particularly in the 41–60 age range, with a notable number presenting in advanced stages (III and IV). These findings are consistent with prior research, reinforcing the connection between diabetes and the advancement of CKD. Furthermore, our study indicates that vitamin D deficiency is more severe in individuals with diabetic CKD compared to those with non-diabetic CKD. A significant association was found between vitamin D insufficiencies and left ventricular mass index (LVMI), indicating that vitamin D status may influence cardiovascular complications in CKD patients. However, while a correlation exists between vitamin D deficiency and LVMI abnormalities, no significant relationship was observed between vitamin D levels and ejection fraction, suggesting that other factors may contribute to cardiac dysfunction in CKD.

Moreover, the patterns of gender distribution and age-related prevalence of chronic kidney disease (CKD) identified in our research are in agreement with global observations, suggesting that CKD is

predominantly found in males and older adults. Our findings underscore the necessity for proactive screening and management of vitamin D deficiency in CKD patients, particularly those with diabetes, to possibly lessen cardiovascular risks. Subsequent studies should investigate the connections between vitamin D, heart function, and CKD advancement to formulate targeted treatment approaches.

### *Declaration by Authors*

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**Conflict of Interest:** The authors declare no conflict of interest.

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