

Original article:

Effect of vitamin D deficiency on cardiac structure and function in patients with predialysis diabetic and non-diabetic chronic kidney disease

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Abstract

Aim: To investigate the relationship between vitamin D levels and cardiac structure and functions in pre-dialysis diabetic and non-diabetic chronic kidney disease(CKD) patients.

Methodology: All the patients under study were selected randomly from medicine and nephrology OPD or admitted in indoor of medicine dept , who have not yet started dialysis and not on vit D supplementation. All were subjected to thorough clinical examination , followed by relevant laboratory investigations. Patients were considered diabetic if they are in insulin , oral hypoglycaemic agents, diagnosed as diet controlled diabetes or had a fasting blood sugar of ≥ 126 mg/dL. - Chronic Kidney Disease were diagnosed according to KDOQI guideline and staging were done using eGFR. -Estimation of Vitamin D level done. -Echocardiography of the selected patient were performed(using M mode)

Results: The present study showed correlation between different stages of vitamin D deficiency and different group of abnormal LVMI in CKD patients. It shows among the CKD patients who are severely vitamin D deficient (stage III) 17 (35.4%) have severely abnormal (group III) LVMI and 5(10.4%) have moderately abnormal LVMI and among moderate vitamin D deficient (stage II) have 112(25%) group II LVMI & 7 (14.58%) have group III LVMI .these relation are statistically significant ($p=0.0163$).From multiple regression analysis it can be conclude that haemoglobin level, eGFR, ejection fraction all can affect LVMI but vitamin D has a statistically significant role.

Conclusion: Chronic kidney disease is associated vitamin D deficiency and abnormal LVMI . Diabetic CKD are more vitamin D deficient and maximum are within age group of 41 to 60 years. Vitamin D deficiency may be associated with widespread risk for CVD in CKD patients.

Keywords: VITAMIN D DEFICIENCY, CARDIAC STRUCTURE PREDIALYSIS DIABETIC

INTRODUCTION

Chronic kidney disease (CKD) is an emerging public health problem and one of the most powerful predictors of premature cardiovascular disease .Vitamin D is a pre-hormone obtained through the diet or via skin synthesis ^{1,2,3}.Cardiovascular (CV) events are common in patients with chronic kidney disease (CKD) but inadequately explained by traditional risk factors. Vitamin D deficiency is highly prevalent in CKD and has been proposed to be a

non-traditional risk factor, but its relationship with cardiac structure is unknown⁴. Emerging evidence suggests that the progression of CKD and many of the cardiovascular complications may be linked to hypovitaminosis D. Patients with CKD have an exceptionally high rate of severe vitamin D deficiency that is further exacerbated by the reduced ability to convert 25-(OH)vitamin D into the active form, 1,25 dihydroxy-vitaminD⁵.

Most patients with CKD do not suffer from symptoms of uremia, nor indeed die from kidney disease. The majority of patients with CKD die from cardiovascular disease, before their kidney dysfunction requires replacement therapy⁶. Cardiovascular disease, defined as the presence of either congestive heart failure (CHF), ischemic heart disease (IHD), or left ventricular hypertrophy (LVH), is prevalent in cohorts with established CKD. Left ventricular hypertrophy (LVH) is highly prevalent in CKD and is associated with a clearly unfavourable prognosis; The incidence of LVH increases with a progressive decline in renal function. Prevalence of LV diastolic dysfunction in CKD is also common¹. Even in the early stages of kidney impairment, the prevalence of LVH is higher than in the general population².

Left ventricular mass is proportional to body size and body surface area. The traditional risk factors for cardiovascular disease such as hypertension, dyslipidemia, diabetes and obesity are highly prevalent in CKD populations⁶. Diabetes mellitus is the leading cause of chronic kidney disease (CKD) and contributes to increased morbidity and mortality in the CKD population⁷.

Wolf and colleagues⁸ found that diabetics were more likely to be severely 25(OH)-vitamin D-deficient (< 10 ng/mL) than non-diabetics (22% vs 17%)⁸. Cardiovascular morbidity and mortality such as congestive heart failure (CHF), ischemic heart disease (IHD), left ventricular hypertrophy (LVH), diastolic dysfunction is prevalent in cohorts with established CKD with vitamin D deficiency. Increasing left ventricular mass index (LVMI) and patients with diastolic dysfunction had poorer prognosis.

There is few study 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.

Aim: To investigate the relationship between vitamin D levels and cardiac structure and functions in pre-dialysis diabetic and non-diabetic chronic kidney disease(CKD) patients.

MATERIALS AND METHODS

1.STUDY AREA:

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

2.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.

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

4.SAMPLE SIZE:

Fifty (50) patients

5.SAMPLE DESIGN:

Simple random selection

6.STUDY DESIGN:

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

7.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 will be assessed by electrochemiluminescence immunoassay.

Fasting Blood Sugar(FBS),Post Pandrial Blood Sugar (PPBS),Urea, creatinine, sodium ,potassium ,calcium ,phosphate, serum uric acid

d).Cardiological parameter:

ECG in all leads

Echocardiography: Left Ventricular dimensions, inter ventricular septalthickness (IVST), left ventricular mass.

Measures of systolic function by ejection fraction .

Measures of diastolic function according to grading

e).Others:

Haematological : Hb, TC, DC,ESR,PLATELET,MCV,MCH ,MCHC,

Urine :for R/E &M/E,C/S

USG of KUB

Chest X-ray

Lipid profile

ANA(where applicable)

METHODS:

-All the patients under study were selected randomly from medicine and nephrology OPD or admitted in indoor of medicine dept , who have not yet started dialysis and not on vit D supplementation. All were subjected to thorough

clinical examination , followed by relevant laboratory investigations. Patients were considered diabetic if they are in insulin , oral hypoglycaemic agents, diagnosed as diet controlled diabetes or had a fasting blood sugar of ≥ 126 mg/dL.

- Chronic Kidney Disease were diagnosed according to KDOQI guideline and staging were done using eGFR.

-Estimation of Vitamin D level done.

-Echocardiography of the selected patient were performed(using M mode) to see the following measurement:

- (i) Size of left ventricular 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(IVST).
- (vii) Diastolic dysfunction assessment

Two methods are available for calculating LV mass from 2D echocardiography: the biplane area-length method and the truncated ellipsoid method. In both methods the LV wall volume is derived by subtracting intra-cavitary (endocardial) LV volume from the entire (epicardial) LV volume including LV walls and ventricular septum. Myocardial mass is equal to the product of the volume and the specific gravity of the myocardium, 1.04g/mL. LV mass can also be estimated from measurements of LV dimension and wall thicknesses on 2D or M-mode echocardiograms.

Left Ventricular Mass index (LVMI) calculated by Devereux's(Penn) formula which is as follows:

$$[1.04\{(IVST+LVID+PWT)^3 - LVID^3\} - 14]g/Body\ Surface\ area^9.$$

According to this criteria LVMI increased if >134 g/m² in men and >110 g/m² in female.

Body surface area will be calculated by the formula: $BSA = (W - 60) \times 0.01 + H$, where BSA is the body surface area in m², W is the weight in kilograms and H is height in meters¹⁰.

LV Ejection Fraction (Dumesnil Method)⁴⁵:

$$LVEF = SV/LVEDV$$

$$LVEDV = (7 * LVEDD^3)/(2.4 + LVEDD)$$

Where,

LVEDD LV end-diastolic diameter

SV Stroke volume

LVEDV LV end-diastolic volume

LVEF LV ejection fraction [%]

Diastolic dysfunction:-

Assessment of diastolic dysfunction should be an integral part of an evaluation of cardiac function because about 50% of patients with heart failure have preserved LVEF. M-mode, two dimensional, and Doppler(blood flow, tissue, and colour) echocardiography are all helpful in evaluating diastolic function.

Diastolic filling is usually classified initially on the basis of the peak mitral flow of the early rapid filling wave (E), peak velocity of the late filling wave caused by atrial contraction (A), E/A ratio, deceleration time (DT) which is the time interval for the peak E to reach zero base line, early diastolic mitral annulus velocity (e') and late diastolic mitral annulus velocity (a').

DETAILS OF SOME INVESTIGATING PROCEDURE:

A) Estimation of blood urea: Method:- Di-acetyl monoxime method for quantitative estimation of urea nitrogen in serum.

Principal: Urea reacts with diacetylmonoxime in hot acid medium producing some pink colour complex. The intensity of the complex is measured colorimetrically at 520 nm (range 510- 540) is proportional to the concentration of urea nitrogen in the specimen under test.

Normal value – urea nitrogen = 10 to 20 mg/dl

Urea = Urea nitrogen x 2.14 = 24- 48 mg/dl

B) Estimation of serum creatinine:

Method: Alkaline picrate method.

Principal: Creatinine is a protein free solute which reacts with alkaline picrate and produces a red coloured complex which is measured colorimetrically.

Normal range: 0.9 – 1.5 mg/dl.

B) Estimated Glomerular Filtration Rate (eGFR):

I have used MDRD formula using android application, details of formula explained previously.

D) Estimation of serum sodium (Na⁺) and potassium (K⁺):

Method used:- Auto analyser (stat profile)

Normal value of Na⁺: 136 – 145 mEq/ml

Normal value of K⁺: 3.5 – 5 mEq/ml

E) Bilirubin and its fraction: Doumas reference method

F) Serum Protein: TP method (Henry's modification of Kingsley's biuret method)

G) Serum Albumin: Bromocresolgreen (BCG) method

H) Complete Haemogram including platelet count: Complete haematoautoanalyser and reports were reviewed under microscopic examination. Normal value of male haemoglobin in male is 13 mg/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.

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. Result are plotted by bar diagram, pi charts where feasible. Chi-Squir test used to analysed non-parametric data and calculation of ‘p’ value, data are also plotted in percentage form wherever needed.

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.

Results:

In our present study , majority of patients were males (62%).M:F ratio was 1.63:1. 24%patients were of the age group 20-40 yrs and 58% were from 40-60yrs and 18% were from more than 60 yrs. Prevalence of diabetic CKD was more (46%) in age group 41 to 60 yrs and non –diabetic CKD in lower age group of 20 -40 yrs (22%). Diabetic CKD patients presented earlier stage (III)(28%) in comparison to non –diabetic CKD which tends to present in later stages (V). Total 56% of all CKD patients were within 41 to 60 years of age group and younger patients tended to present in later stages where older patients in stages of CKD .

Diabetic CKD patients were more severe deficient in vitamin D than non-diabetic CKD. p value was 0.04 so correlation is stastistically significant.

Left ventricular Mass Index(LVMI) of each CKD pt assessed as described in methodology. LVMI is classified as normal, mild ,moderately and severely abnormal as in reference 25,26.Here, group I is reffered as mildly abnormal, group II as moderately abnormal and group III as severely abnormal LVMI.

STAGE OF DM CKD	EF<50%	EF≥50%
STAGE III	6(18.75%)	8(25%)
STAGE IV	3(9.37%)	4(12.5%)
STAGE V	4(12.5%)	7(21.87%)
TOTAL(n=32)	13(40.6%)	19(59.4%)

TABLE 1, shows that the correlation is statistically insignificant($p=0.9$).so, EF is not related to stages of DM-CKD patients.

STAGE OF NON-DM CKD	EF<50%	EF≥50
STAGE III	1(5.5%)	1(5.5%)
STAGE IV	2(11%)	4(22.2)
STAGE V	3(16.6%)	7(38.9)
TOTAL(n=18)	6(33.3%)	12(66.7%)

TABLE 2 SHOWING CORRELATION BETWEEN EJECTION FRACTION AND DIFFERENT STAGES OF NON- DIABETIC CKD.

GRADE OF VIT D DEFICIENY IN DM CKD PATIENTS	EF<50% n(%)	EF≥50% n (%)
GRADE I	0	3(9.37%)
GRADE II	4(12.5%)	6(18.75%)
GRADE III	9(28.12%)	10(31.25%)
TABLE (n=32)	13(40.62%)	19(59.38%)

TABLE 3 SHOWING RELATION OF EJECTION FRACTION WITH GRADE OFVITAMIN D DEFICIENCY IN DIABETIC CKD PATIENTS .VALUES ARE STATISTICALLY INSIGNIFICANT (P=0.2) .

GRADE OF VIT D DEFICIENCY IN NON-DM CKD	EF<50% n(%)	EF≥50% n (%)
GRADE I	2(11.1%)	1(5.6%)
GRADE II	2(11.1%)	9(50%)

GRADE III	2(11.1%)	2(11.1%)
TOTAL(n=18)	6(33.3%)	12(66.7%)

TABLE 4 SHOWING RELATION OF EJECTION FRACTION WITH GRADE OF VITAMIN D DEFICIENCY IN DIABETIC CKD PATIENTS .

It shows that table is statistically insignificant.(p=0.2)

GRADE OF VIATAMIN D DEFICIENCY	NO DD n(%)	DD PRESENT n(%)
GRADE I	1(3.1%)	2(6.25%)
GRADE II	10(31.2%)	2(6.25%)
GRADE III	12(37.5)	5(15.62%)
TOTAL	23(71.87%)	9(28.12%)

TABLE 5 SHOWING RELATION BETWEEN GRADE OF VITAMIN D DEFFICIENCY WITH DIASTOLIC DYSFUNCTION IN DIABETIC CKD PATIENTS.

Table 6 Showing correlation between left ventricular mass index and vitamin deficiency by ANOVA

Vitamin D Level	Standard Error	95% CI
➤ 30ng/ml	8.012	99.75-104.94
10-30 ng/ml	6.19	126.34-152.16
<10 ng/ml	6.08	142.29-167.54

P value =0.021

Multiple Comparisons by post Hoc using Tukey HSD significant LVMI is seen I CKD between vitamin D level > 30 and <10 ng/ml group with significance 0.026

Table 7 shows correlation between different parameters affecting LVMI and Vitamin D status.

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 (2-tailed).

- There is significant correlation between eGFR and LVMI related inversely.
- There is significant correlation between Vitamin D level and LVMI related inversely.
- There is significant correlation between eGFR and vitamin D level.
- No significant correlation between haemoglobin level and LVMI.

Multiple regression analysis was carried out using back ward selection method, regression criteria being $p \geq 0.05$ with vitamin D ,eGFR, ejection fraction and haemoglobin as predictor with LVMI as regressor.

Table 8 Variable Entered/Removed^b

Model	Variable Entered	Variable Removed	Method
1	Haemoglobin(Hb), Ejection fraction(EF), Vitamin D, eGFR ^a		Enter
2		Hb	Backward (criterion: Probability of F-to- remove $\geq .050$)
3		EF	Backward (criterion:

			Probability of F-to-remove >= .050).
4		eGFR	Backward (criterion: Probability of F-to-remove >= .050).

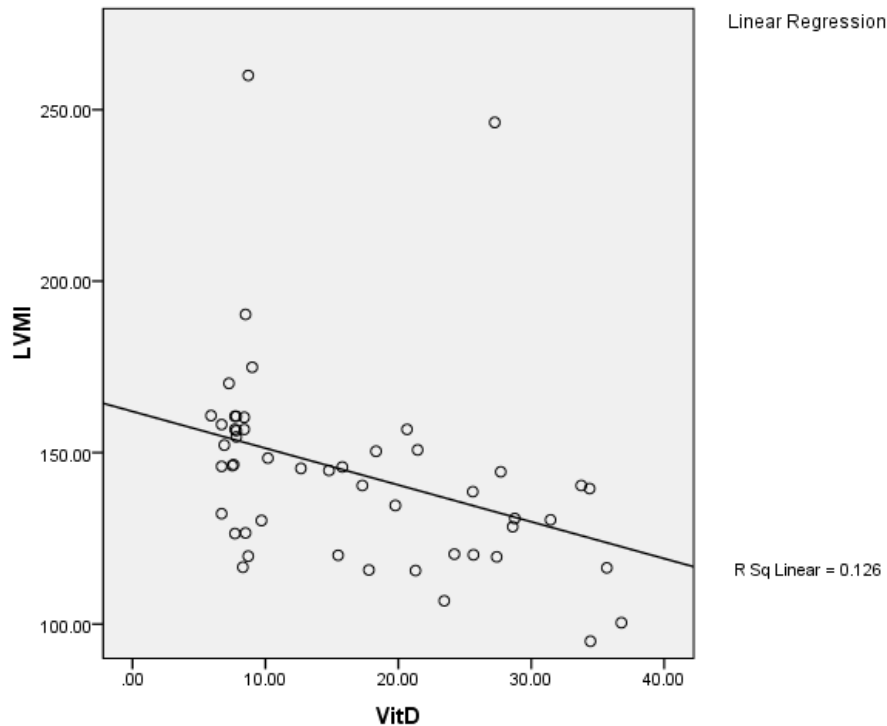
a= All requested variables entered.

b= Dependent Variable: LVMI

Table 9

Coefficients^a

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	128.238	37.233		3.444	.001
	eGFR	-.450	.349	-.199	-1.292	.203
	VitD	-.905	.434	-.300	-2.085	.043
	EF	.802	.590	.183	1.358	.181
	Hb	-.229	2.228	-.015	-.103	.919
2	(Constant)	126.463	32.632		3.875	.000
	eGFR	-.463	.321	-.205	-1.442	.156
	VitD	-.902	.428	-.299	-2.106	.041
	EF	.801	.584	.182	1.371	.177
3	(Constant)	169.504	9.008		18.818	.000
	eGFR	-.519	.322	-.229	-1.611	.114
	VitD	-.826	.429	-.274	-1.927	.060
4	(Constant)	162.009	7.841		20.661	.000
	VitD	-1.073	.407	-.356	-2.635	.011



In summary of multiple regression it can be conclude that haemoglobin level , eGFR , Ejection fraction , all can affect LVMI but vitamin D have also definite role.

DISCUSSION

The present study was done with 50 patients with clinical, biochemical and radiological features of chronic kidney disease admitted in various units of the Medicine department of NRS Medical College & Hospital through a period from Decembar;2011 to July ;2013 and revealed the following epidemiological information.

In present study showed correlation between different stages of vitamin D deficiency and different group of abnormal LVMI in CKD patients. It shows among the CKD patients who are severely vitamin D deficient (stage III) 17 (35.4%) have severely abnormal (group III) LVMI and 5(10.4%) have moderately abnormal LVMI and among moderate vitamin D deficient (stage II) have 112(25%) group II LVMI & 7 (14.58%) have group III LVMI .these relation are statistically significant ($p=0.0163$).From multiple regression analysis it can be conclude that haemoglobin level, eGFR, ejection fraction all can affect LVMI but vitamin D has a statistically significant role.

Conclusion:

Chronic kidney disease is associated vitamin D deficiency and abnormal LVMI . Diabetic CKD are more vitamin D deficient and maximum are within age group of 41 to 60 years. Vitamin D deficiency may be associated with widespread risk for CVD in CKD patients. It is evident by grossly abnormal LVMI in severely vitamin D deficient CKD patients in my study. Though cardiac function (ejection fraction and diastolic dysfunction) in CKD patients are not related with state of vitamin D deficiency in my study it may be due to small sample size. A significant determinant of LVH (abnormal LVMI) are age , blood pressure and anaemia

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