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VITAMIN D LEVEL AND OTHER BIOCHEMICAL PARAMETERS OF MINERAL BONE DISORDERS AND ITS ASSOCIATION WITH LEFT VENTRICULAR MASS AND DIASTOLIC DYSFUNCTION IN YOUNG NON-DIABETIC ADULT PATIENTS WITH CHRONIC KIDNEY DISEASE

Nephrology

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ABSTRACT

Introduction: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD). Chronic kidney disease (CKD) associated cardiovascular mortality is seen higher in diastolic heart failure and it is an early predictor.

Hypovitaminosis D is extensively being studied as a nontraditional risk factor for CVD. The aim of the present study is to look into the association of vitamin D and other parameters of mineral bone disorder (MBD) with diastolic dysfunction and left ventricular mass (LVM) in non-diabetic young adult patients with CKD.

Materials and Methods: The present study was a hospital based cross sectional observational study in patients attending nephrology unit ,ikdrc.Group I and II consisted of non-diabetic pre-dialysis CKD (stage 4 & 5) patients and healthy controls respectively. Group IA and IB consisted of cases with diastolic dysfunction and cases without diastolic dysfunction respectively. Vitamin D level was measured by Enhanced chemiluminescence method and iPTH by ElectroChemiluminescence method. Parameters for diastolic function and left ventricular mass was assessed by Doppler echocardiography, tissue Doppler imaging and M-mode echocardiography.

Results: Vitamin D level was significantly lower in group I as compared to group II. Diastolic dysfunction was present in 48.84% among cases. Diastolic dysfunction was significantly associated with calcium phosphorous product but not with vitamin D. A statistically significant positive correlation between LVMI and iPTH was found in our study.

Conclusions: Calcium phosphorous product can be better predictor for diastolic dysfunction than Vitamin D and hence early predictor of cardiovascular mortality in pre-dialysis CKD patients.

KEYWORDS

vitamin D, chronic kidney disease, left ventricular mass, cardiovascular, calcium phosphorous product

INTRODUCTION:

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD) (1). Chronic kidney disease (CKD) associated mortality is seen higher in diastolic heart failure (2,3). Diastolic heart failure is a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction (EF) and abnormal diastolic function. Early manifestation results in diastolic dysfunction and increase in left ventricular mass (LVM) (4,5). The increased prevalence of cardiovascular disease in CKD patients derives from both traditional ("classic") and nontraditional (CKD-related) risk factors. Hypovitaminosis D is extensively being studied as a nontraditional risk factor for CVD owing to its increase prevalence in patients with CKD (6). Vitamin D apart from maintaining calcium, phosphorus and parathyroid hormone (PTH) homeostasis, (7-9) appears to play a more extensive role as a cell differentiating and ant proliferative factor with actions in a variety of tissues including the renal, cardiovascular, and immune system (9-11).Vitamin D deficiency prevails in epidemic proportions all over the Indian subcontinent, with a prevalence of 70%–100% in the general population (12). Hence in this study we looked for vitamin D and other biochemical parameters of mineral bone disorder (MBD) and their association with diastolic dysfunction and LVM in non-diabetic young adult patients with CKD.

PATIENTS AND METHODS: The present study was a hospital based cross sectional observational study in patients attending nephrology unit at **ikdrc** over a period of one year. Forty three non-diabetic pre-dialysis CKD (stage 4 & 5), patients between age 12-40 years (Group I) and forty healthy controls (age & sex matched) (Group II) were enrolled after giving informed consent. The study was approved by the ethical committee of the university and informed consent was taken from patients and it confirms to the provision of Declaration of Helsinki (as revised in Tokyo 2004). Group I was further divided as Group IA consisting of cases with diastolic dysfunction and Group IB had cases without diastolic dysfunction. Patients with severe anemia (Hb <6.0 g/dL), or taking erythropoiesis stimulating agents, known malignancy, heart failure (ejection fraction <40%) were excluded. None of the study subjects were smokers nor on vitamin D therapy. Conditions that may influence collagen metabolism such as recent (<6months) surgery or trauma, fibrotic diseases or active inflammatory conditions or patients on immunosuppressive medications or presence of arteriovenous fistula for dialysis access were not enrolled. None of the above had previous acute coronary event. Study population was evaluated for vitamin D levels, intact parathyroid hormone (iPTH) and echocardiography. Cases were grouped on the basis of vitamin D level. For the purposes of analysis, vitamin D concentration was categorized based on current Kidney Disease Outcomes Quality Initiative guidelines (K/DOQI guidelines, 2003) as optimal level (>30 ng/mL), insufficient level (15 - 30 ng/mL) and deficient level (<15 ng/mL). We measured vitamin D (25-OH D3) levels as per the instruction provided with the kit of ---------- by Enhanced chemiluminescence method and iPTH by ElectroChemiluminescence method. Paramaters for diastolic function and left ventricular mass was assessed by Doppler echocardiography, tissue Doppler imaging and M-mode echocardiography. Diastolic dysfunction was observed in cases with CKD, according to the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE) guidelines for assessment of diastolic function by echocardiography.

Statistical analysis of the data was performed on SPSS (Statistical Package for Social Science) for Windows version 16.0. Appropriate parametric (student t test, independent samples t test) and correlation tests were used to analyze data sets.

RESULTS: The mean age of CKD patients in group I was 32.1 ± 7.5 years (range 13-40) while that of healthy control group II was 29.6 ± 4.8 years (range 23-40). All cases were found to be hypertensive (>140/90 mm Hg) as compared to control group. Serum protein and albumin were significantly lower in group I as compared to group II. Mean Vitamin D level was significantly less in group I (14.6 ± 6.4 ng/mL) as compared to group II (16.4 ± 4.7 ng/mL) (p<0.001). Mean value of log iPTH in cases was found to be 2.3 ± 0.7 pg/mL as compared to controls 1.2 ± 0.3 pg/mL and the difference was statistically significant(p<0.003). Mean Vitamin D level was less in group I (14.61±6.46 ng/ml) as compared to group II (16.47+4.74 ng/ml) (p<0.001).In group I, 58.1% of cases had vitamin D deficiency (<15 ng/mL) whereas in group II, 50% had vitamin D deficiency. It is to be noted that Vitamin D level was less than 30 ng/mL in all the cases as well as controls. Cases had a higher mean Left Ventricular Mass Index (LVMI) than controls (70.3 vs 23.8) (p<0.001)

Out of 43 cases, nearly in half the number of cases, diastolic dysfunction was present (48.8% vs 51.1%). None of the healthy controls had diastolic dysfunction irrespective of vitamin D level. Although vitamin D deficiency (<15) was found in higher proportion in group IA (66.7%) as compared to group IB (50.0%). However this difference was not found to be statistically significant (p=0.26) (Table 1). Comparision of different biochemical parameters among cases shown in Table……. An inverse correlation between LVMI and vitamin D was found but it was statistically not significant (Fig.2).

However on contrary Serum Phosphate level was found as an significant risk factor for development of diastolic dysfunction (p=<0.005) while with Calcium-phosphorus product (>55mg2/dl2) it was (p=<0.05).(table……) A statistically significant positive correlation between LVMI and iPTH was found in our study.

DISCUSSION:

Vitamin D is associated with diabetic CKD in adults but our study for the first time shows the relationship of vitamin D in young non-diabetic patients. 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-vitamin D. Emerging evidence suggests that the progression of CKD and many of the cardiovascular complications may be linked to hypovitaminosis D (13,14).Moreover in CKD patients with further decrease in glomerular filteration rate (GFR) there is also secondary hyperparathyroidism with hypocalcemia and hyperphosphotemia. Levin et al. in their study on 175 patients with progressive renal disease found that age was significantly different between the groups with and without left ventricular hypertrophy (55.4 ± 15.9 vs 49.2 ± 14.5 years respectively) (14).Young adults were included in the study group to remove the confounding factor of older age as a risk for cardiovascular changes. Modification of the biochemical or echocardiographic parameters by age related morbidities like diabetes mellitus, hypertension etc. is thought to be less in study involving young population. In our study Vitamin D level was significantly lower in cases as compared to controls. This is similar to that reported by Kari et al (2012) (15). …….16

In this current study, there was no significant association between vitamin D deficiency and diastolic dysfunction in CKD patients (p=0.26), which was in accordance to study reported with Pandit et al. (17). Another study also reported that lower Vitamin D levels were not associated with any of the biochemical, conduction, or echocardiographic outcomes in subjects who were free of cardiovascular disease at baseline (18).These results are in contrary to that observed in a study on 34 children with CKD, which showed that LVMI correlated with vitamin D (r = -0.54; p<0.05) and serum-intact parathyroid hormone (iPTH) levels correlated with diastolic dysfunction [E/E' ratio (r = 0.63; p < 0.05) and E' (r = -0.61; p < 0.05)] (19). Hence variable results regarding this association have been observed in different studies. Further large scale studies are needed to find any true association between vitamin D levels and diastolic dysfunction.

In this current study, mean Left Ventricular Mass Index (LVMI) was significantly higher in cases (70.31 ± 29.80 $g/m^{2.7}$) than in controls (23.8 ± 9.05 $g/m^{2.7}$). This was consistent with other studies (31-33) showing increase prevalence of left ventricular hypertrophy in CKD patients. Patange et al. (17) in a study on 34 children with CKD, showed that LVMI inversely correlated with vitamin D and it was also statistically significant (r = -0.54; p < 0.05), whereas in our study we did not found significant correlation. Another study showed no clinically significant improvement on administration of vitamin D in patients with CKD (34).

We observed a mean level of serum phosphate as 7.3 ± 2.4 mg/dL and 5.5 ± 1.4 mg/dL in cases with and without diastolic dysfunction respectively. It was found to be a significant risk factor for development of diastolic dysfunction in cases with CKD (p<0.005). Another study showing positive relation between hyperphosphatemia and increased cardiovascular morbidity has also been shown by Galetta et al. in uremic patients on maintenance haemodialysis (20).Similar results were observed by Block et al. (21), Tentori et al. (22), Gutierrez et al. (23) in their respective studies. Elevated serum phosphorus is a predictable accompaniment of end-stage renal disease (ESRD) in the absence of dietary phosphate restriction or supplemental phosphate binders. The consequences of hyperphosphatemia include the development and progression of secondary hyperparathyroidism and a predisposition to metastatic calcification when the product of serum calcium and phosphorus (Ca x PO4) is elevated. Both of these conditions may contribute to the substantial morbidity and mortality seen in patients with ESRD.(Ren Fail. 2001 Jan;23(1):115-26.). A significant association between Calcium Phosphorus product (>55 mg2/dl2) and diastolic dysfunction was found (p=0.03) in our study which is similar to a study reported by Strozecki et al. (27), Regmi P et al. (28). Hyperphosphatemia leading to deranged mineral bone metabolism have adverse effects on left ventricular function.

In our study, using correlation analysis with LVMI as an outcome of interest, intact parathyroid hormone (iPTH) was found to be an important predictor showing linear relationship, which was statistically significant (r=0.47, p<0.05). Similar results were obtained by Ha et al. (35) in their study on 62 pre-dialysis chronic renal failure patients. Also Al-Hilali et al. found positive correlation between iPTH and LVMI in their study on 130 patients on hemodialysis (36).This may be due to a potential role of iPTH in Intermyocardiocytic fibrosis, i.e., nonreparative interstitial fibrosis with collagen fiber deposition, commonly found in uremic patients and animals as seen by Amann et al. (37) in their study.

CONCLUSION:

Vitamin D deficiency prevails in CKD patients as well as in healthy population. CKD patients have lower mean Vitamin D as compared to healthy age and sex matched controls. All healthy control despite being vitamin D deficient, did not have diastolic dysfunction on echocardiography. Vitamin D deficiency was not statistically significant for diastolic dysfunction or LVMI in CKD patients. However, calcium phosphorous product is better predictor for diastolic dysfunction and hence early predictor of cardiovascular mortality in pre-dialysis CKD patients. Secondary hyperparathyroidism may be a bad prognostic marker of cardiovascular morbidity and mortality due to left ventricular hypertrophy in CKD.

CONFLICTS OF INTEREST: None

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Conflicts of Interest: None

Table 1: Association of Vit D levels between Group IA and Group IB cases

Vit D	Diastolic dysfunction (Group IA) (n=21)		No diastolic dysfunction (Group IB) (n=22)		Statistical significance
	No.	%	No.	%	'p' value
Vit D <15ng/mL	14	66.7	11	50.0	0.268
Vit D ≥15ng/mL	07	33.3	11	50.0	

Vit D – vitamin D, Group IA - cases with diastolic dysfunction, Group IB - cases without diastolic dysfunction.

Table 2: Association between Calcium Phosphate Product levels and Diastolic Dysfunction

CaPO4 product	Diastolic dysfunction (Group IA) (n=21)		No diastolic dysfunction (Group IB) (n=22)		Statistical significance
	No.	%	No.	%	'p' value
CaPO4<55 mg2/dl2	12	57.1%	19	86.4%	0.033*
CaPO4 >55 mg2/dl2	09	42.9%	03	13.6%	

*-significant, Group IA - cases with diastolic dysfunction, Group IB - cases without diastolic dysfunction.

Fig 1: Scatterplot showing the linear relationshipbetween serum intactPTH and LVMI
LVMI – left ventricular mass index, iPTH –intact parathyroid hormone

Fig 2: Scatter plot showing relationship, LVMI and vit D levels.
LVMI – left ventricular mass index, Vit D – vitamin D

Table 11: Haematological/biochemical variables between Group IA and Group IB (Between Group Differences)

Variable	Group IA (n=21)	Group IB (n=22)	'P' value
	Mean ± SD	Mean ± SD	
Haemoglobin (gm/dl)	7.0 ± 1.6	7.8 ± 1.9	0.177

S.Potassium(mmol/l)	5.0 ± 1.2	4.5 ± 0.8	0.094
S.Protein(mg/dl)	6.2 ± 1.0	6.3 ± 0.7	0.920
S.Albumin (mg/dl)	3.6 ± 0.7	3.8 ± 0.6	0.493
S.Calcium (mg/dl)	7.7 ± 1.4	8.1 ± 1.6	0.559
S.Phosphate (mg/dl)	7.3 ± 2.4	5.5 ± 1.4	0.003*
S.Uric acid (mg/dl)	8.0 ± 2.5	7.6 ± 2.9	0.878
B. urea (mg/dl)	181.4 ± 83.4	148.5 ± 65.5	0.203
S.Creatinine (mg/dl)	9.7 ± 4.8	8.5 ± 3.7	0.540
GFR (ml/min/m2)	14.1 ± 24.3	10.6 ± 5.7	0.891
iPTH (pg/ml)	433.54 ± 328.61	353.12 ± 317.91	0.419
log iPTH (pg/ml)	2.35±0.75	2.24±0.71	0.640

GFR- glomerular filteration rate i PTH- intact parathyroid hormone *significant

Serum phosphate was found to be an important predictor (p=0.003) in cases, whereas rest of the variables did not show any significant association.

Table 12: Serum lipid profile between Group IA and Group IB (Between Group Differences)

Variable	Group IA (n=21)	Group IB (n=22)	'P' value
	Mean ± SD	Mean ± SD	
T.Cholesterol (mg/dl)	148.3±37.05	134.58±29.33	0.184
Triglycerides(mg/dl)	157.29±74.82	131.68±4.51	0.178
LDL (mg/dl)	75.01±30.69	66.82±25.07	0.344
VLDL (mg/dl)	31.57±15.03	26.58±8.82	0.189
HDL(mg/dl)	42.78±13.33	41.77±10.09	0.781

LDL- low density lipoprotein VLDL- very low density lipoprotein HDL- high density lipoprotein

There was no significant difference in any of the lipid profile variable between Group IA and Group IB.

Table 13: Association of Vitamin D levels between Group IA and Group

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