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RESEARCH ARTICLE

Relationship between Hypovitaminosis D and Cardiac Abnormalities in Pre Dialysis Chronic Kidney Disease

Maria Carolina Neves[1,2], Luís Sette[1], Mônica Becker[3], Lucila Valente[1,2] and Brivaldo Markman Filho[2,3]*

[1]*Nephrology Service, Clinics Hospital, Federal University of Pernambuco (UFPE), Recife, Brazil*

[2]*Graduate Program in Health Sciences, Federal University of Pernambuco (UFPE), Recife, Brazil*

[3]*Cardiology Service, Clinics Hospital, Federal University of Pernambuco (UFPE), Recife, Brazil*

***Corresponding author:** *Maria Carolina Neves, Nephrology Service and Graduate Program in Health Sciences, Clinics Hospital, Federal University of Pernambuco , Av. Professor Moraes Rego, 1235 - Cidade Universitária, Recife - PE, Brazil, 50670-901, Tel: 558121263734*

Abstract

Background: The presence of structural and functional changes in the left ventricle (LV) are good predictors of cardiovascular events in patients with chronic kidney disease (CKD) and are associated with decreasing renal function. Studies in CKD patients on hemodialysis evidenced associations of serum 25-OH vitamin D (vit D) with myocardial function and structural changes. However, it is not known whether serum vit D is associated with Doppler echocardiogram (ECHO)-based cardiac changes in patients with CKD managed conservatively.

Hypothesis: Hypovitaminosis D is associated with ECHO-based cardiac changes in patients with CKD managed conservatively.

Methods: This cross-sectional study included patients with CKD managed conservatively at a reference nephrology outpatient clinic. CKD stage was classified according to the KDIGO guidelines. The glomerular filtration rate was estimated by the CKD-EPI equation. Serum vit D was classified as insufficient/deficient when < 30 ng/mL and as normal when ≥ 30 ng/mL. ECHO-based cardiac changes were classified according to the American Society of Echocardiography criteria.

Results: Serum vit D was measured in 137 of the 141 study patients, and 112 patients underwent ECHO. The mean age was 58.8 ± 16.0 years. Most patients were female and 80% self-reported being non-blacks. In multivariate analysis, insufficient/deficient serum vit D levels were independent risk factors for changes in ventricular geometry (OR: 3.85; p = 0.041) and reduced LV ejection fraction (OR: 1.06; p = 0.044), when compared to normal vit D serum levels.

Conclusion: In patients with CKD managed conservatively, hypovitaminosis D is independently associated with structural and functional changes in the heart.

Keywords

Vitamin D, Chronic kidney failure, Echocardiography transthoracic, Ventricular function, Ventricular remodeling

Introduction

Chronic kidney disease (CKD) is a severe global health problem, and its prevalence is increasing. It is characterised by progressive and irreversible renal function [1,2]. The main cause of death in patients with CKD is cardiovascular disease (CVD), which is associated with many traditional risk factors: Hypertension, left ventricular hypertrophy (LVH), diabetes mellitus (DM), atherosclerosis, smoking, dislipidemia and old age [3,4].

Traditional risk factors alone do not explain the high mortality observed in these patients [5]. Hence, other risk factors, called nontraditional, have been receiving more attention, such as inflammation, hyperphosphatemia, hyperparathyroidism, anemia, microalbuminuria and hypovitaminosis D [6].

Structural and functional cardiac changes are frequently diagnosed by transthoracic Doppler echocardiogram (ECHO). The presence of left ventricule (LV) structural and functional changes are good predictors

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of cardiovascular events in patients with CKD and are associated with decreasing renal function [7].

Animal studies indicate that serum vitamin D (vit D) affects myocardial geometry and function [8]. In fact, vit D receptors have been identified in the cardiac muscle, and a decrease in their activity in mice is associated with cardiomyocyte hypertrophy, causing LVH in mice [9-11]. In addition to low receptor activity, hypovitaminosis D increases circulating renin and blood pressure. Likewise, studies in humans with chronic heart failure (CHF) have found associations of serum vit D with myocardial function and cardiac structural changes, that is, individuals with low vit D have worse left ventricular function and higher final diastolic diameter [12,13]. Nonetheless, no study has specifically investigated whether serum vit D is associated with ECHO-based cardiac changes in patients with CKD managed conservatively.

Given that hypovitaminosis D can lead to cardiac dysfunction and those patients with CKD have high CVD mortality, the objective of this study was to assess whether low serum vit D is associated with ECHO-based cardiac changes in patients with GFR < 60 mlmin/1.73 m^2 managed conservatively.

Methods

A cross-sectional study was conducted from December 2014 to July 2015 with CKD patients managed conservatively at the CKD outpatient clinic of a tertiary hospital. The patients were selected by spontaneous and consecutive demand as they arrived at the clinic. Patients who took vit D or selective vit D receptor activators in the last three months were excluded.

The study was approved by the Research Ethics Committee of the institution.

The patients signed an informed consent form and answered a questionnaire about demographic, anthropometric, and clinical data. Two 5 mL samples of blood were collected from each patient. These samples were centrifuged and stored at -80 °C until analysis.

The biochemical tests were done by the automated kinetic method in the chemical analyzer Labmax 240 and included: Vit D, creatinine, fasting glucose, total cholesterol and fractions, calcium, phosphorus, parathyroid hormone (PTH), hemoglobin, and alkaline phosphatase.

Vit D: Assays performed on equipment Abbot Architect immunoassay microparticle chemiluminescence. Serum vit D was classified as insufficient/deficient when < 30 ng/mL and as normal when ≥ 30 ng/mL.

The GFR was estimated by the equation Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) through measures of serum creatinine [14-17]. CKD stage was classified according to GFR as instructed by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines in: GFR 45-59 mL/min/1.73 m^2 stage 3a; 30-44 mL/min/1.73 m^2 stage 3b; 15-29 mL/min/1.73 m^2 stage 4 and < 15 mL/min/1.73 m^2, stage 5 [18].

The patients underwent transthoracic ECHO using the device Vivid I (GE Medical Systems Israel, Ultrasound, Ltd. Tirat Hacarmel, Israel) with a 2.5 mHz transductor. The ECHO measurements followed the criteria established by the American Society of Echocardiography [19]. The changes in LV structure were evaluated through Doppler ECHO. As for the geometric pattern of the LV, it was considered as an alteration the presence of any one of the following changes: *Concentric remodeling:* Left ventricular mass index less than 115 g/m^2 for men and less than 95 g/m^2 for women with relative wall thickness greater than 0.42. *Concentric left ventricular hypertrophy:* Left ventricular mass index greater than 115 g/m^2 for men and more than 95 g/m^2 or women with relative wall thickness greater than 0.42. *Excentric left ventricular hypertrophy*: Left ventricular mass index greater than 115 g/m^2 for men and more than 95 g/m^2 for women with relative wall thickness less than 0.42 [20]. The data were stored in a Microsoft Office Excel 2007®.

Statistical Analysis

The patient's categorical sociodemographic and clinical variables were presented as relative and absolute frequency distributions. The Shapiro-Wilks test determined whether the quantitative variables had normal distribution. Variables with normal distribution were expressed as mean and standard deviation, and variables without normal distribution, as median and interquartile range.

The Pearson's chi-square test for proportions compared the cardiovascular risk factors and serum vit D. Analysis of variance (ANOVA) with Bonferroni correction compared the means, and the Kruskal-Wallis test compared the medians.

The statistically significant variables ($p < 0.05$) related to cardiovascular risk with respect to serum vit D were eligible for adjustment of the association between vitD and ECO-based cardiac changes. The association was adjusted by a multivariate logistic regression model. The measure of association odds ratio (OR) was estimated for each of the ECHO measurements, which were then analyzed independently.

The confounders were tested and removed from the final model according to statistical significance and/or biological plausibility. The data were treated by the software Stata version 12.0.

Results

Serum vit D was measured in 137 of the 141 study patients, and 112 patients underwent ECHO. The patient's mean age was 58.8 ± 16.0 years. Most patients were female and 80% self-reported being non-blacks. Table 1 shows the other demographic data, CKD etiolo-

Table 1: Profile of the study population according to demographic, cardiovascular risk, kidney disease characteristics and serum 25-OH vitamin D.

Characteristics	n = 141
Demographic	
Age[a]	58.8 ± 16.0 years
Gender	
Male	66 (45.3%)
Female	75 (54.7%)
Race	
Non-black	114 (81.0%)
Black	27 (19.0%)
Cardiovascular risk-related factors	
BMI[a]	27.0 ± 5.3 Kg/m^2
Obesity	29 (22.0%)
Inactivity	104 (78.2%)
Smoking: smoker or ex-smoker	48 (35.6%)
Hypertension	122 (89.1%)
DM	48 (35.3%)
CAD	20 (14.7%)
History of stroke	20 (14.7%)
Dyslipidemia	85 (62.0%)
Family history of CAD	15 (11.0%)
Chronic kidney disease etiology	
DM	37 (27.0%)
Hypertension	38 (27.7%)
Glomerulopathy	27 (19.7%)
ADPKD	7 (5.1%)
CPN	9 (6.6%)
Indeterminate	9 (6.6%)
Others	10 (7.3%)
Chronic kidney disease stage	
3a	17 (12.4%)
3b	27 (19.7%)
4	68 (49.6%)
5	25 (18.3%)
Serumvit D (ng/mL)[a]	24.31 ± 9.51
SerumVit D (ng/mL) classification	
Insufficient/deficient (< 30)	109 (79.6%)
Normal (> 30)	28 (20.4%)

[a]Mean ± standard deviation.

Abbreviations: BMI: Body mass index; DM: Diabetes mellitus; CAD: Coronary artery disease; ADPKD: Autosomal dominant polycystic kidney disease; CPN: Chronic pyelonephritis; vit D: 25-OH vitamin D.

gy, CKD stage and serum vit D.

As shown in Figure 1, CKD stages were significantly associated with vit D insufficiency/deficiency, that is, as kidney failure increased, the odds of finding hypovitaminosis D in CKD stages 4 (OR: 3.30; 95%CI: 1.05 - 10.4; p = 0.042) and 5 (OR: 6.29; 95%CI 1.29 - 30.5; p = 0.023) also increased.

Table 2 shows the ECHO characteristics of the patients by serum vit D.

The associations between serum vit D and ECHO variables were adjusted for the confounders shown in Table 3. All of them are known cardiovascular risk factors. The variables gender, BMI, DM, serum hemoglobin, cholesterol, PTH, calcium, albumin, and GFR were associated with low serum vit D. Thus, the variables eligible for the multivariate model of the association between serum vit D and ECHO changes were analyzed in Table 4.

Insufficient or deficient serum vit D was associated with ECHO-related cardiac changes. Patients with low serum vit D were 3.85 times more likely to have ventricular geometry changes (OR: 3.85; p = 0.041) and reduced ejection fraction (OR: 1.06; p = 0.044) than patients with normal serum vit D (Table 4).

Discussion

Insufficient/deficient serum vit D was significantly associated with reduced LVEF and changes in ventricular geometry even after adjustment for the traditional CVD risk factors in patients with GFR < 60 mL/min/1.73 m^2.

These results agree with those reported by other cross-sectional studies of patients with congestive heart failure (CHF), which found that vitamin D deficiency was associated with lower LVEF [12,21]. Moreover, another study of CHF patients found that patients with low serum vit D had greater final systolic diameter and lower fractional shortening than patients with higher serum vit D [13], which agrees with the present analysis. Low final diastolic and systolic volumes and better fractional shortening were also observed after micronutrient supplementation, including vit D, in older adults with CHF [22].

In a community study, Fall, et al. found a significant association between higher serum vit D and smaller LV final systolic diameter, and better fractional shortening and LVEF even after adjusting for cardiovascular risk factors [23]. Their patients were older, had normal kidney function, and only 10% were diabetic, unlike the present study patients.

LVH, the most common cardiac change in patients with CKD, is associated with high mortality [24]. LV remodeling describes the process by which the size, geometry, and function of the heart change over time [19]. In CKD patients without symptomatic heart disease, development of the progressive concentric pattern in the LV is common and not consistently related to traditional risk factors, including hypertension and anemia [25]. This observation suggests that nontraditional cardiovascular risk factors, such as hypovitaminosis D, may play a role in the development of concentric LVH.

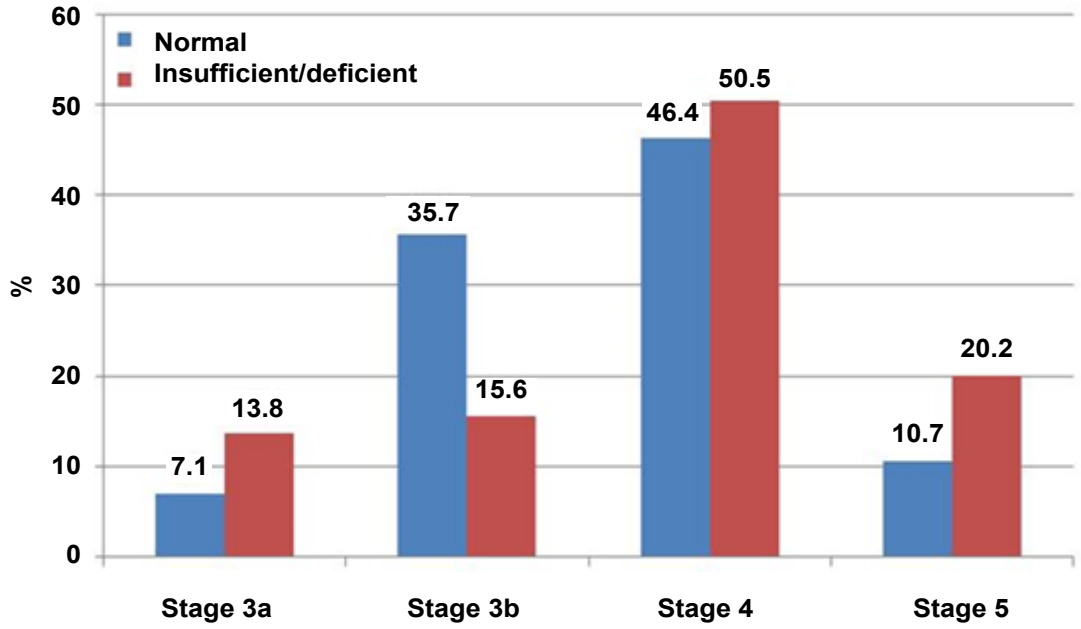

Figure 1: Association between serum 25-OH vitamin D and chronic kidney disease stages.

Table 2: Association between serum 25-OH vitamin D and Doppler echocardiogram measurements in patients with chronic kidney disease.

Doppler echocardiogram variables	Serum 25-0H vitamin D		OR (IC 95%)	*p*-valor
	Normal (n = 22)	Insufficient/Deficient (n = 89)		
Diastolic function				
No	8 (25.0%)	25 (29.4%)	Reference	-
Yes	24 (75.0%)	60 (70.6%)	0.8 (0.32 - 2.02)	0.637
Systolic function				
No	32 (100%)	78 (91.8%)	Reference	-
Yes	0 (-)	7 (8.2%)	Not calculated	0.094
Ventricular geometry				
Normal	19 (59.4%)	39 (45.9%)	Reference	-
Changed	13 (40.6%)	46 (54.1%)	1.72 (0.76 - 3.93)	0.195
Ventricular geometry				
Normal	14 (63.6%)	42 (46.7%)	Referência	-
Concentric hypertrophy	5 (22.7%)	26 (28.9%)	1.73 (0.56 - 5.37)	0.341
Eccentric hypertrophy	2 (9.1%)	8 (8.9%)	1.33 (0.25 - 7.04)	0.735
Concentric remodeling	1 (4.5%)	14 (15.6%)	4.67 (0.56 - 38.8)	0.154
Valvular dysfunction				
Yes	29 (90.6%)	74 (87.1%)	Reference	-
No	3 (9.4%)	11 (12.9%)	1.44 (0.37 - 5.52)	0.598
Heart chamber measurements				
Left atrial volume (mL/m^2)	43 (34.5; 50)	45 (37; 54)	1.01 (0.99 - 1.03)	0.377
Left ventricular mass (g)	136 (118; 172)	164 (127; 219)	1.004 (0.99 - 1.01)	0.118
Mass index (g/m^2)	80 (73.5; 105)	100 (76; 120)	1.01 (0.99 - 1.02)	0.084
Ejection fraction	71.4 ± 7.3	68.5 ± 10.4	0.97 (0.92 - 1.01)	0.148

*Statistically significant association ($p < 0.05$).

Table 3: Association between serum 25-OH vitamin D and cardiovascular risk factors in patients with chronic kidney disease.

Cardiovascular risk factors	Serum 25-0H vitamin D		*p*-value
	Normal (n = 28)	Insufficient/deficient (n = 109)	
Demographic			
Age	59.1 ± 16.2	57.5 ± 15.3	0.633
Gender			
Male	17 (60.7%)	45 (41.3%)	0.065
Female	11 (39.3%)	64 (58.7%)	
Race			
Non-black	22 (78.6%)	89 (81.6%)	0.711
Black	6 (21.4%)	20 (18.4%)	
Cardiovascular risk factors			
BMI[a]	25.5 ± 4.7	27.4 ± 5.5	0.092
Obesity	2 (7.1%)	27 (26.0%)	0.033*
Inactivity	19 (70.4%)	85 (80.2%)	0.270
Hypertension	25 (89.3%)	97 (89.0%)	0.964
DM	6 (21.4%)	42 (38.9%)	0.085
CAD	3 (11.1%)	17 (15.6%)	0.556
History of stroke	7 (25.9%)	14 (13.0%)	0.096
Dyslipidemia	15 (53.6%)	70 (64.2%)	0.300
Laboratory findings			
Hemoglobin [a b]	12.77 ± 1.88	11.45 ± 1.68	0.004*
Cholesterol[a c]	157 (125; 176)	174 (151; 206)	0.028*
PTH[a]	176 (107; 277)	261 (160; 382)	0.060
Calcium[a]	9.43 ± 0.57	9.09 ± 0.65	0.015*
Phosphorus	3.79 ± 1.45	4.10 ± 1.20	0.324
Albumin[c]	4.05 ± 0.46	3.93 ± 0.52	0.391
AP	75 (55; 97)	90 (69; 117)	0.203
Creatinine	2.21 (1.9; 3.1)	2.50 (1.9; 3.8)	0.434
GFR	26.6 ± 8.9	25.0 ± 11.8	0,501

*Statistically significant association ($p < 0.05$); [a]Statistically significant difference between the normal and deficient groups ($p < 0.05$); [b]Statistically significant difference between the normal and insufficient groups ($p < 0.05$); [c]Statistically significant difference between the insufficient and deficient groups ($p < 0.05$).

Abbreviations: BMI: Body mass index; CAD: Coronary artery disease; ADPKD: Autosomal dominant polycystic kidney disease; CPN: Chronic pyelonephritis; Vit D: 25-OH vitamin D; PTH: Parathyroid hormone; AP: Alkaline phosphatase; GFR: glomerular filtration rate.

A cross-sectional study of 61 patients with CKD on hemodialysis found an association between hypovitaminosis D and LVH, even in the absence of high PTH [26]. According to the study, the patients had mean serum vit D of 23 ng/mL, mean age of 61 years, and roughly one-third of the sample was diabetic, characteristics similar to those of the present study sample. However, the patients studied by Bucharles, et al. [26] were on hemodialysis, which is associated with higher prevalences of hypovitaminosis D and cardiac changes.

Intervention studies corroborate the hypothesis that hypovitaminosis D affects myocardial function and structure. In CKD patients with elevated serum PTH, analogous treatment with vit D resulted in myocardial hypertrophy regression, and better systolic blood pressure and diastolic cardiac function [27]. More recently, a study with patients on hemodialysis, including patients with a history of cardiomyopathy taking activated vitamin D, cholecalciferol replacement in patients with low serum vit D reduced LV mass, suggesting improvement in specific cardiovascular risk markers [28].

A recent randomized clinical trial (VINDICATE, VitamIN D treatIng patients with Chronic heArTfailurE) with 229 patients assessed the long-term efficacy of vit D supplementation in patients with CHF caused by LV systolic dysfunction [29]. The authors found significantly better cardiac function (LVEF increased by 6.07%; 95%CI 3.20-8.95; $p < 0.0001$) and LV remodeling reversion (-2.49 mm; 95%CI -4.09 to -0.90; $p < 0.002$) in the one-year follow-up of patients given vit D [29]. None of their

Table 4: Multivariate analysis of the association between serum 25-OH vitamin D and Doppler echocardiogram measurements in patients with chronic kidney disease.

Doppler echocardiogram variables	Insufficient or Deficient OR (95% CI)	p-value**
Diastolic failure		
No	Reference	-
Yes	0.44 (0.12 - 1.69)	0.234
Ventricular geometry		
Normal	Reference	-
Changed	**3.85 (1.06 - 14.1)**	**0.041***
Heart chamber measurements		
Left atrial volume (mL/m^2)	1.02 (0.99 - 1.05)	0.202
Left ventricular mass (g)	1.00 (0.99 - 1.01)	0.355
Mass index (g/m^2)	1.01 (0.99 - 1.02)	0.373
Reduced ejection fraction	**1.06 (1.01 - 1.13)**	**0.044***

*Statistically significant association ($p < 0.05$); **Association adjusted for gender, body mass index, diabetes, and parathyroid hormone.

patients had CKD, the mean serum vit D (14 ng/mL) was lower than the present mean, the patients were older (mean age of 68 years), and fewer were diabetic (21%), when compared to this study.

On the other hand, Pilz, et al. assessed 648 patients and did not find association of serum vit D with LV geometry or myocardial function [30]. The mean age of the patients was 67 years, and none of the patients had CKD.

Another study that did not find an association between low serum vit D and myocardial function or ventricular geometry was the multicentric clinical trial PRIMO (Paricalcitol Capsule Benefits in Renal Failure–Induced Cardiac Morbidity), which assessed the beneficial effects of paricalcitol on LVH in 227 patients with CKD (GFR < 60 mL/min/1.73 m^2) managed conservatively [31]. Patients with mild to moderate LVH failed to reduce LV mass after 48 weeks of daily paricalcitol supplementation, but the number of hospitalizations decreased, a secondary variable of interest of the study [31]. The negative results may stem from the sample size, considered small, or by the effect of inadequate blood pressure control, a factor that increases LVH.

The present study is the first to assess whether vit D is associated with changes in LV geometry and myocardial function in CKD patients managed conservatively. Hypovitaminosis D may play an important role in the development of structural and functional changes in the heart of CKD patients managed conservatively. Serum vit D determination and supplementation, when necessary, should be considered in CKD patients managed conservatively to reduce cardiovascular complications.

Although, this study did not assess hospital readmission and mortality rates, it is important to emphasize the association of low EF and ventricular geometry changes with worse CHF prognosis.

Study Limitations

The study has some limitations. It was conducted in a single center, and its cross-sectional cohort design only allows for the generation of hypotheses. The sample size was small.

Prospective multicentric studies with a higher number of patients in each CKD stage are needed. Such studies should also assess other variables and potential confounders in this group of patients.

Conclusion

The present study found that low serum vit D was related to reduced LVEF and ventricular geometry changes, factors that contribute to cardiovascular mortality. Therefore, our findings corroborate the hypothesis that vit D can be a marker of structural heart disease in patients with CKD and GFR < 60 mL/min/1.73 m^2.

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