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Hypovitaminosis D Is Associated with Systemic Inflammation and Concentric Myocardial Geometric Pattern in Hemodialysis Patients with Low iPTH Levels

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Key Words
Cardiovascular disease · Hemodialysis · Inflammation · Vitamin D

Abstract
Background: Vitamin D [25(OH)D] deficiency is a cardiovascular risk factor in the hemodialysis (HD) population. The aim of this study was to identify hypovitaminosis D in HD patients without signs of hyperparathyroidism and to analyze its association to inflammation and echocardiographic alterations. ***Methods:*** Patients on HD with iPTH <300 pg/ml not receiving vitamin D therapy were recruited. Hypovitaminosis D was defined as 25(OH)D <30 ng/ml. High-sensitivity C-reactive protein, interleukin-6 and serum albumin were used as inflammation markers. Echocardiograms were performed in an interdialytic mid-week day. ***Results:*** Sixty-one patients (mean age of 56 ± 15 years, 52% males, 93% Caucasians, 31% diabetic) were included, and 75% presented hypovitaminosis D. Inflammation was more prevalent among those with hypovitaminosis D, and these patients presented higher relative wall thickness (0.48 ± 0.11 vs. 0.42 ± 0.10 mm; p = 0.05) and lower left ventricular diastolic (49.8 ± 6.2 vs. 54.7 ± 5.8 mm; p = 0.013) and systolic (31.9 ± 5.7 vs. 36.8 ± 7.2 mm; p = 0.012) diameters. ***Conclusions:*** Hypovitaminosis D is associated with inflammation and concentric geometric pattern of the left ventricle, even in the absence of high iPTH levels. Vitamin D repletion (aiming to reduce cardiovascular complications) should also be considered in HD patients with normal or low iPTH levels.

Introduction

Cardiovascular disease is the leading cause of death in chronic kidney disease (CKD) patients [1], and although traditional cardiovascular risk factors (hypertension, diabetes, dyslipidemia) are frequent in the dialysis population, the pathogenesis of cardiovascular disease in CKD involves the interplay of traditional risk factors and uremia-related factors, such as mineral metabolism disorders [2] and systemic inflammation [3].

Vitamin D receptors (VDR) are found ubiquitously throughout the body, and most tissues and many cells possess the enzymatic mechanism to convert the primary circulating form of vitamin D, 25 hydroxyvitamin D_2 (calcidiol) into the active form 1,25 dihydroxyvitamin D_3

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(calcitriol) which acts through a nuclear receptor to carry out its many functions, related to mineral metabolism and several noncalcemic actions [4]. Local calcitriol production depends on the level of circulating 25(OH)D, which is the barometer for vitamin D status. Patients with CKD in all stages have a high prevalence of hypovitaminosis D [5, 6], and there is preliminary evidence from observational studies suggesting beneficial cardiovascular effects of vitamin D therapy in uremia [7, 8]. The reasons for these associations are largely unknown and may be related to the impact of the lack of VDR activation in the cardiovascular system.

From the cardiovascular viewpoint, hypovitaminosis D appears to predispose to hypertension, left ventricular hypertrophy (LVH), congestive heart failure, and chronic vascular inflammation [9]. First, a state of systemic inflammation, commonly assessed by serum C-reactive protein levels is observed in approximately 40–50% of patients in end-stage renal disease and associations between inflammation and cardiovascular mortality are well documented in medical renal literature [10]. Today, biomarkers of inflammation are considered important tools to monitor cardiovascular risk. The interplay between vitamin D and systemic inflammation is observed in experimental models, in which cytokine production may be related to vitamin D action upon monocytes and macrophages, modulating the immunological system, and thus determining a more anti-inflammatory profile of cytokine network [11, 12]. Second, LVH is the most frequent cardiac alteration in CKD patients [13], and this pathological condition in uremia has been described as a complex myocardiopathy with peculiar causes and consequences in the myocardial structure that include fibrosis, apoptosis and capillary degeneration. The pathogenesis of LVH has been extensively studied in uremia, and although traditional risk factors such as fluid overload, hypertension and anemia are among the most important, alone these factors cannot fully explain the changes observed in the uremic myocardium. Hypovitaminosis D is an important candidate since it acts as a negative endocrine regulator of renin-angiotensin synthesis, which induces not only hypertrophy, but also inflammatory changes in the myocardium, that may lead to cardiac fibrosis [14, 15].

Until recently, traditional guidelines recommended measuring 25(OH)D levels in CKD stages 3 and 4 only if iPTH levels were elevated, and no guidelines were given for measuring hypovitaminosis D in dialysis CKD patients, particularly in patients presenting low iPTH levels [16]. Although there has been a recent recommendation to monitor and treat hypovitaminosis D in CKD despite signs of hyperparathyroidism, this recommendation does not find support in clinical studies until the present [17]. We hypothesize that hemodialysis (HD) patients may present a more pronounced inflammatory response and uremic cardiomyopathy even in the presence of low iPTH levels. Thus, the aim of this study was to identify hypovitaminosis D in HD patients with low iPTH levels and to analyze its association with systemic inflammation and echocardiographic parameters.

Material and Methods

The study population consisted of 384 patients followed in four dialysis units under the same management and clinical protocols. All adult patients with iPTH <300 pg/ml, no previous history of cardiovascular disease (to avoid the myocardial consequences of coronary artery disease, vascular peripheral disease and chronic heart failure) were eligible for inclusion. Patients presenting systemic inflammatory diseases (systemic lupus erythematosus), acute (urinary tract infections, pneumonia, vascular access infections) or chronic infectious conditions (tuberculosis) and malignancy were excluded from the study, based on their clinical conditions and medical history.

The study was carried out during the months of April, May and June 2009 (late fall and winter) in Curitiba, Brazil. All patients were submitted to 4-hour, three times weekly HD sessions, with polysulfone membranes and bicarbonate dialysate. Dialysis dose was delivered to achieve a Kt/V above 1.2. Hemoglobin levels were monitored to achieve K/DOQI-recommended parameters. None of the patients were receiving vitamin D therapy for at least one year or were naïve to vitamin D supplementation. All patients except one received antihypertensive therapy (55% angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, 50% calcium channel blockers). Sevelamer (34%) or calcium carbonate (66%) was used as phosphate binders. Blood pressure was evaluated immediately before all midweek HD sessions (average of 4 measurements) in the month of biochemical and echocardiographic analysis. Pulse pressure (PP) was calculated using the formula PP = SBP – DBP, on the basis of blood pressure evaluated shortly before the HD sessions simultaneously to the collection of samples and the echocardiographic evaluation. All patients were submitted to a standardized study protocol previously approved by the ethics committee of our institution. All patients signed an informed consent before entering the study.

Blood Chemistries

All blood samples in our study were obtained immediately before the midweek dialysis session, on average 15 days before the echocardiographic analysis, and included determination of serum albumin, hemoglobin, alkaline phosphatase, serum high-sensitivity C-reactive protein (hs-CRP), serum phosphate and calcium. Interleukin-6 (IL-6) was measured by the ELISA technique and hs-CRP by nephelometry [3]. Inflammation was defined when hs-CRP was >3 mg/l (following the American Heart Association to define patients at high risk of cardiovascular disease). Serum parathormone (iPTH 1–84) was measured by radioimmunoassay (normal levels range 12–65 pg/ml).

Since the major circulating metabolite of vitamin D is 25(OH) D, levels of this substance were used to determine adequacy of vitamin D stores. Serum 25(OH)D was determined by the chemiluminescence method DiaSorin LIAISON 25OH Vitamin D assay [18], with an intra-assay and interassay coefficients of variability of, on average, 4 and 6%, respectively [19]. 1,25 dihydroxyvitamin D levels were determined by radioimmunoassay (1,25-Dihydroxyvitamin D RIA KIT; DiaSorin). Hypovitaminosis D was defined when 25(OH)D levels were <30 ng/ml (deficiency <20 ng/ml and insufficiency when 21–29 ng/ml). Levels ≥30–60 ng/ml were defined as normal [4]. Levels of 1,25 dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] were considered normal when ≥15.8 pg/ml and deficient when <15.8 pg/ml (as indicated by the manufacturer).

Echocardiographic Analysis

Echocardiograms were performed on the interdialytic day, mid-week, between 8 a.m. and 1 p.m., as previously recommended [20]. The same experienced cardiologist (S.H.B.) performed all examinations using a commercially available ultrasound system (Envisor CD Phillips Ultrasound) equipped with a 2.5-MHz transducer. According to the Penn convention [21], linear measurements were obtained from M-mode calculations. The LV mass was calculated [22] and indexed by height in meters at the power of 2.7 ($height^{2.7}$), diagnosing LVH when >51 g/$height^{2.7}$ [22]. The combination of LV mass index and relative wall thickness (2 × mean wall thickness/LV diastolic diameter) defined four LV geometric patterns: normal geometry, concentric remodeling, eccentric and concentric LVH. Relative wall thickness reference cutoff value 0.45 [23, 24] separated eccentric (below) from concentric (above) LVH. Concentric remodeling was defined by normal LV mass plus increased relative wall thickness. Ejection fraction was calculated by Simpson's method and Doppler mitral flow velocities were recorded from the apical four-chamber view, as recommended by the American Society of Echocardiography [23].

Peak early (E) and atrial (A) transmitral velocities, E/A ratio, and deceleration time of early diastolic filling were measured. TDI of annular mitral velocities were obtained with a small (2-mm) sample volume placed sequentially at the septal and lateral junction of the LV wall with the mitral annulus [25]. Early (E′) and late (A′) diastolic mitral annulus velocities, E′/A′ ratio, and E/E′ ratio displayed in our study, represent the mean value between the two sites. All velocities and intervals were averaged over three cardiac cycles. Diastolic dysfunction was defined by: (1) E/A <1; (2) E/A >2; or (3) E/A between 1 and 2 with concomitant E/E′ >10. Left atrial volume was determined using the two-dimensional biplane Simpson's method [24]. Measurements were done in end systole, and indexed both to BSA (LAVi-BSA) and $height^{2.7}$ (LAVi-$height^{2.7}$) [26]. Normal LAVi-BSA has been determined to be 22 ± 6 ml/m^2; however, a cutoff value of 32 ml/m^2 was indicative of major cardiovascular risk [27].

Statistical Analyses

Patients with vitamin D deficiency and insufficiency, based on 25 hydroxyvitamin D levels, were studied in the same group and compared with patients with normal vitamin D levels. All tests were performed using JMP Windows 8.0 (SAS Institute Inc., USA). Data are expressed as means ± SD or median, depending on the distribution. Univariate Pearson correlation coefficients were used to assess the relationship among biochemical parameters. Proportions were compared by χ^2 test. To compare means in two different groups, we used the Student's t test or the Mann-Whitney test. The kappa coefficient test was used to assess agreement between 2 continuous variables. Multivariate analysis was performed with the objective of evaluating the impact of hypovitaminosis D on echocardiographic variables. We considered a p value ≤0.05 as statistically significant.

Results

Patient Characteristics

The baseline clinical and biochemical characteristics of our patients are reported in table 1. Out of the original population, 61 patients fulfilled the inclusion criteria. These patients were on HD for at least 3 months (median 23; range 3–50 months) and had hypertension (36%), diabetes mellitus (31%), chronic glomerulonephritis (19%), polycystic kidney disease (6%) and other causes (4%) as their primary kidney disease. There were 46 patients with hypovitaminosis D and 15 patients with normal vitamin D levels.

When we compared patients with and without hypovitaminosis D (table 1), there were no differences in mean age, time on dialysis, prevalence of hypertension (95% in each group) and hemoglobin levels (11.8 ± 1.5 vs. 12.1 ± 2.0 g/dl). Additionally, there were no differences in serum levels of calcium (9.1 ± 0.7 vs. 9.4 ± 0.7 mg/dl), phosphorus (4.6 ± 1.1 vs. 4.7 ± 1.8), alkaline phosphatase (81.4 ± 32.3 vs. 67.8 ± 24.4 UI/l), iPTH (134 ± 76 vs. 141 ± 84 pg/ml) and $1,25(OH)_2D_3$ levels (21.8 ± 10.7 vs. 23.0 ± 16.6 pg/ml; p = NS); however, there was a significant difference in 25(OH)D mean levels (17.8 ± 6.2 vs. 40.7 ± 6.2 ng/ml; $p < 0.001$) and in the prevalence of diabetes (41 vs. 13%; $p < 0.05$). In addition, there were no statistical differences in systolic blood pressure mean levels, prevalence of angiotensin receptor blocker and angiotensin converting enzyme prescription and number of antihypertensive drugs in use in each group analyzed. Diastolic blood pressure mean levels were, additionally, higher in the normal vitamin D group (p = 0.03; table 1). PP was not significantly different between the two groups of patients (table 1).

Serum 25(OH)D and $1,25(OH)_2D_3$ did not correlate (overall agreement cases 41%, kappa coefficient <0.4) and serum 25(OH)D was below the recommended sufficiency values in 75% of our HD patients, which was more frequently observed in diabetics and females. Fourteen patients were classified as insufficient for vitamin D 'status' and 32 patients had vitamin D deficiency (levels below 20 ng/ml). No correlation was found between 25(OH)D lev-

Table 1. Baseline clinical and biochemical characteristics of the study population

Variable	Total population (n = 61)	Vitamin D deficit (n = 46)	Vitamin D normal (n = 15)	p value[1]
Age, years	56 ± 15	56.6 ± 15.6	54.2 ± 13.6	0.59
Male, %	52	39	73	0.03
Caucasian, %	93	91	100	0.56
Mean time in HD, months	19	17	24	0.29
Diabetic, %	31	41	13	<0.05
SBP, mm Hg	136 ± 16	140 ± 12	135 ± 17	0.33
DBP, mm Hg	83 ± 7	81 ± 7	86 ± 5	0.03
PP, mm Hg	53 ± 13	52 ± 14	55 ± 9	0.35
Body mass index	23.5 ± 4.0	23.6 ± 4.0	23.3 ± 4.3	0.82
Hemoglobin, g/dl	12.2 ± 3.4	11.8 ± 1.5	12.1 ± 2.0	0.50
Angiotensin receptor blocker, %	17	15	27	0.43
Angiotensin conversion enzyme inhibitor, %	37	43	20	0.13
Number of antihypertensive drugs	1.50 ± 0.94	1.50 ± 0.8	1.53 ± 1.1	0.81
Mineral metabolism parameters				
Serum calcium, mg/dl	9.2 ± 0.7	9.1 ± 0.7	9.4 ± 0.7	0.15
Serum phosphate, mg/dl	4.9 ± 1.4	4.6 ± 1.1	4.7 ± 1.8	0.76
iPTH, pg/ml	139 ± 82	134 ± 76	141 ± 84	0.78
Alkaline phosphatase, UI/l	78 ± 30	81.4 ± 32.3	67.8 ± 24.4	0.11
25 hydroxyvitamin D_3, ng/ml	23.4 ± 11.7	17.8 ± 6.2	40.7 ± 6.2	<0.001
1,25 dihydroxyvitamin D_3, pg/ml	22.1 ± 12.3	21.8 ± 10.7	23.0 ± 16.6	0.74
Inflammatory markers				
Serum albumin, g/dl	4.23 ± 0.47	4.1 ± 0.5	4.3 ± 0.3	0.14
hs-CRP, mg/l	0.53 (0.05–29.6)	0.61 (0.05–29.6)	0.29 (0.06–15.5)	0.13
IL-6, pg/ml	6.78 (0.99–19.5)	6.46 (1.36–19.58)	8.77 (0.99–19.5)	0.53

Data expressed as means ± SD or median (range).
[1] Vitamin D deficit (hypovitaminosis D) versus vitamin D normal groups.

els and iPTH, calcium and phosphate levels. In addition, no correlation was observed between 25(OH)D levels and body mass index.

Inflammation Biomarkers and Vitamin D Status

Systemic inflammation based on hs-CRP >3 mg/l was observed in 67% of our population (41 patients, 20 men and 21 women). The proportion of inflamed (hs-CRP >3 mg/l) patients among those with 25(OH)D deficit was higher (73%) when compared to 25(OH)D-repleted patients (43%, $\chi^2 = 3.9$; $p < 0.05$; fig. 1). Accordingly, there was a positive correlation between serum albumin and 25(OH)D in plasma ($r = 0.34$; $p = 0.007$). Although there was a strong correlation between hs-CRP and IL-6 ($r = 0.71$; $p < 0.001$), when these variables were studied as continuous, IL- 6 levels did not correlate with 25(OH)D levels. When we compared patients with normal $1,25(OH)_2D_3$ levels with patients with $1,25(OH)_2D_3$ deficit, we did not observe any statistically significant difference in hs-CRP (median 0.39 vs. 0.97 mg/l; $p = 0.06$) and IL-6 (median 6.11 vs. 8.22 pg/ml; p = 0,40), but there was a significant difference in albumin levels (4.3 ± 0.3 vs. 3.9 ± 0.4 g/dl; $p < 0.01$).

Echocardiographic Parameters and Vitamin D Status

LVH was observed in 84% of the study sample, systolic dysfunction in 16%, diastolic dysfunction in 68% and valvular calcification in 20% (table 2). Patients with hypovitaminosis D presented lower LV diastolic (49.8 ± 6.2 vs. 54.7 ± 5.8 mm; $p = 0.013$) and systolic (31.9 ± 5.7 vs. 36.8 ± 7.2 mm; $p = 0.012$) diameters as well as higher relative wall thickness (0.48 ± 0.11 vs. 0.42 ± 0.10; $p = 0.05$) compared to patients with normal levels of 25(OH)D (fig. 2, 3). There were no differences regarding 25(OH)D deficit in patients with or without systolic dysfunction, diastolic dysfunction and valvular calcification. Finally, there was no association between LV mass index and 25(OH)D status (table 2).

Table 2. Echocardiographic parameters evaluated in the study population

Variable	Entire population (n = 61)	Vitamin D deficit (n = 46)	Vitamin D normal (n = 15)	p value[1]
Systolic dysfunction, %	16	11	29	0.195
Diastolic dysfunction, %	68	74	64	0.505
Relative wall thickness, mm	0.46 ± 0.10	0.48 ± 0.11	0.42 ± 0.10	0.050
Systolic left diameter, mm	33.2 ± 6.3	31.9 ± 5.7	36.8 ± 5.8	0.013
Diastolic left diameter, mm	50.9 ± 6.3	49.8 ± 6.2	54.7 ± 7.2	0.012
LVH, %	84	84	86	1.0
Valvular calcification, %	20	20	14	1.0
Left ventricular mass, g/m^2	172 ± 74	167 ± 61	177 ± 57	0.590

Data expressed as means ± SD. [1] Vitamin D deficit versus vitamin D normal groups.

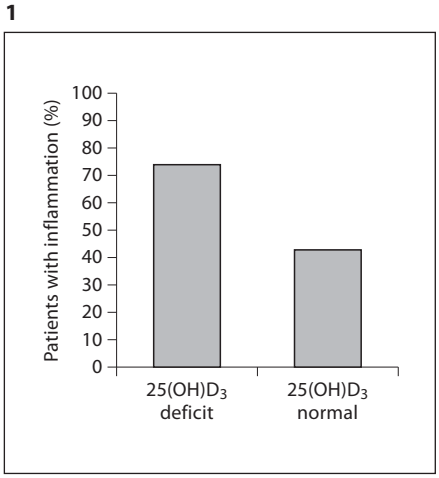

Fig. 1. Proportion of patients with inflammation (hs-CRP >3 mg/l) among patients with and without 25(OH)D_3 deficit (p = 0.031).

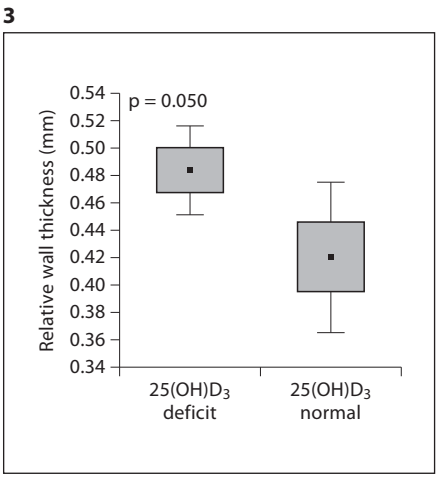

Fig. 3. Relative wall thickness in patients with and without vitamin D deficit (mean ± SE, 95% CI).

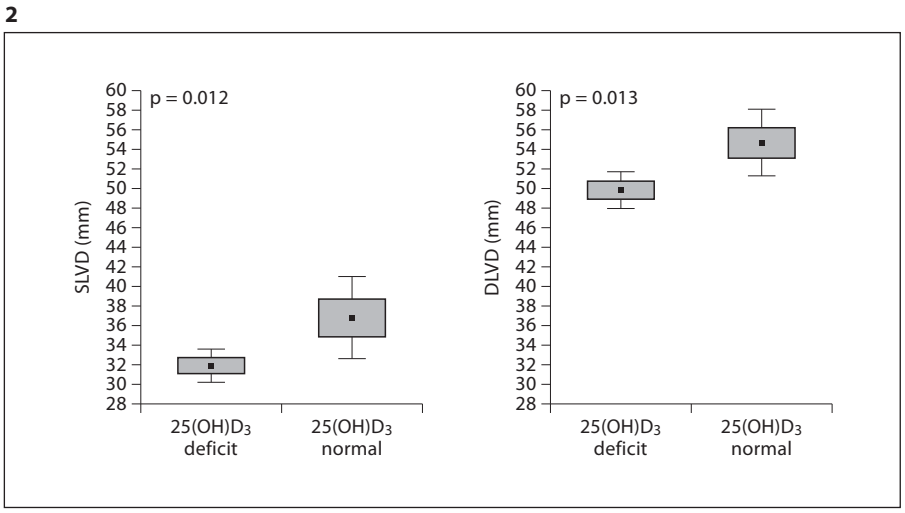

Fig. 2. Systolic (SLVD) and diastolic (DLVD) LV diameters in patients with and without 25(OH)D_3 deficit (mean ± SE, 95% CI).

After adjustment for age, female gender and diabetes, the presence of hypovitaminosis D was still associated with lower LV systolic diameter ($p = 0.003$) and a trend toward relative wall thickness ($p = 0.06$). The same echocardiographic parameters studied did not correlate with $1,25(OH)_2D_3$ levels when we compared patients with $1,25(OH)_2D_3$ deficit with those with normal levels.

Discussion

Vitamin D deficiency has recently emerged as a cardiovascular risk factor in CKD by mechanisms that are not fully understood, but that may involve inadequate VDR activation on cardiovascular tissue [28, 29] and in the immune system. The main results of our study indicate that hypovitaminosis D may be related to more pronounced systemic inflammation and to LV concentric geometric pattern in a selected group of HD patients with low iPTH levels and no previous history of cardiovascular disease.

According to several studies performed in CKD patients, both those on dialysis (including the present study) and non-dialysis patients, there is a very high prevalence of hypovitaminosis D [5, 6, 30], and our findings agree with them. This high prevalence can be explained in part by the presence of risk factors for vitamin D deficiency among dialysis patients such as decreased appetite, dietary restrictions, and decreased sunlight exposure. We observed a high prevalence of hypovitaminosis D among female gender when compared to males, which was observed by others [5]. There is no definitive explanation for this finding, although hormonal differences may be implicated. No study until now has addressed this issue focusing on the population with low iPTH levels, a population that is not routinely screened for hypovitaminosis D according to traditional guidelines [16]. Only recent guidelines [17] recommend the measurement of 25(OH)D levels in CKD stage 3–5 and dialysis patients, independent of iPTH levels, and replacement with ergocalciferol or cholecalciferol in those who present hypovitaminosis D. It is important to point out that there is no consistent background information supporting the need for screening of hypovitaminosis D in the dialysis population with low iPTH and its association with asymptomatic cardiovascular disease and inflammation. Our results support the active screening of hypovitaminosis in all patients with CKD due to the high prevalence and potential cardiovascular consequences (discussed bellow) of hypovitaminosis D in the absence of mineral metabolism disorders.

We observed not only a high prevalence of hypovitaminosis D, but also an association between inflammation and vitamin D deficiency in HD patients. In our study, we found a positive correlation between 25(OH)D levels and serum albumin, which was in accordance with previous findings [5, 31]. Additionally, we observed a significant association between hypovitaminosis D and hs-CRP levels >3 mg/l, reinforcing the association of vitamin D deficit with systemic inflammation in HD patients. Similarly, a recent study [31] performed in HD patients reported that $25(OH)D_3$ levels were negatively correlated with CRP levels and positively correlated with albumin levels, findings that are in accordance with our results. However, it is important to point out that, while in the present study patients were not receiving any form of vitamin D therapy for at least one year, in their study 47% of the population were using activated vitamin D. Moreover, in that study, there were 29% of patients with definitive coronary artery disease, including patients with past acute myocardial infarction, a clinical condition that could determine LV geometric abnormalities, different from our population who had no past documented history of coronary artery disease.

Systemic inflammation is frequently observed in dialysis patients, and this abnormality is a significant predictor of death in this population [10]. Although many factors are responsible for this state of inflammation in the dialysis population, hypovitaminosis D represents an unrecognized (and potentially reversible) factor playing a role in the generation of this inflammatory state. Indeed, some intriguing connections between systemic inflammation and vitamin D deficiency emerged from experimental studies in which vitamin D could potentially generate a better profile of cytokine network, reducing the expression of such biomarkers as IL-6, IL-1 and IFN-γ and promote upregulation of the anti-inflammatory cytokine IL-10 [11, 12, 32]. The association between hypovitaminosis D and inflammation observed in the present study may indicate that the correction of this disturbance may be an anti-inflammatory therapy, with potential benefits in the immune and cardiovascular system. This hypothesis needs to be tested in intervention studies.

LVH is the most frequent abnormality observed in CKD patients and is associated with high mortality [13]. Although LVH has been traditionally linked to myocardial hypertrophy (i.e. due to hypertension), in uremia it has been described as a complex myocardiopathy with peculiar causes and consequences in the myocardial structure that include fibrosis, apoptosis and capillary degeneration leading to remodeling. Some studies evalu-

ated the long-term evolution of cardiomyopathy in peritoneal dialysis patients [33] and in HD patients [34], and found that LV mass increased during long-term follow up, but mass-to-volume ratios increased more significantly, suggesting that progressive wall thickening was the primary evolutionary pattern. The common association between concentric hypertrophy and myocardial fibrosis as a consequence of pressure load has been proposed in the uremic population [35].

Myocardial disease in uremia may be related to vitamin D deficiency, as observed in some animal models, by increasing myocardial collagen content and indirectly through calcium, altering myosin protein expression, inducing impaired cardiac contractility [15]. Vitamin D plays a role in cardiac cell contraction, proliferation, differentiation, and furthermore it may play a role in the maintenance of vascular tone and cardiac output [36]. Decreased VDR activity increased renin levels and blood pressure and has caused LVH in experimental models, which will undergo inflammatory changes mediated by angiotensin that will induce fibrosis as a result of the inflammatory process [14, 36].

LV remodeling describes the process by which the heart changes its size, geometry and function over time [24]. In HD patients with no symptomatic cardiac disease, the development of a progressive concentric LV geometric pattern was common and not consistently related to traditional risk factors including arterial hypertension and anemia [37]. This observation points to the fact that nontraditional cardiovascular risk factors, such as hypovitaminosis D, could play a role in the development of concentric left ventricle hypertrophy. The characteristics of our study design, which excluded patients with past history of cardiovascular disease, reinforce the finding that the structural changes in the myocardium of the patients are potentially related to the decrease in VDR activation, and do not represent consequences of the baseline disease.

In our study, we observed reduced LV dimensions and increased relative wall thickness in patients with hypovitaminosis D, findings that are related to an altered concentric geometric pattern of the left ventricle (which includes concentric remodeling and concentric hypertrophy). The fact that patients with hypovitaminosis D present a distinct geometric echocardiographic pattern points to the fact that these differences may be due to the lack of activation of cardiac VDR. Interestingly, patients with and without hypovitaminosis D presented similar prevalence of comorbidities (including hypertension), hemoglobin and concomitant treatment. Moreover, the echocardiographic abnormalities observed were still present after the adjustment for gender, age and diabetes, although differences in relative wall thickness among our two groups did not reach statistical significance. Based on these findings and the strict selection criteria (low iPTH and no history of cardiovascular disease), we suggest that the echocardiographic findings of a distinct geometric pattern in patients with hypovitaminosis D may be related to an early stage of uremic myocardiopathy, in which hypovitaminosis D potentially may play a pivotal role.

Intervention studies corroborate our hypothesis that hypovitaminosis D has myocardial consequences. In CKD patients with high iPTH levels, treatment with a vitamin D analogue resulted in regression of myocardial hypertrophy and improvement in cardiac systolic and diastolic function [38]. More recently, in a study of HD patients (including those receiving activated vitamin D and with previous cardiomyopathy), cholecalciferol supplementation in vitamin D-deficient HD patients resulted in attenuation of inflammation and reduced LV mass, suggesting improvements in specific markers of cardiovascular risk in CKD [39].

In summary, patients with hypovitaminosis D present more pronounced inflammation and signs of LV concentric remodeling, even in HD patients with low iPTH levels and with no symptomatic cardiovascular disease. We hypothesize that, due to its pathogenic potential and based on our preliminary results, hypovitaminosis D (independent of PTH) may play a role in the progression of the structural changes of the heart in CKD patients. Hypovitaminosis D screening and repletion should also be considered in HD patients with normal and low iPTH levels with the aim to reduce cardiovascular complications.

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