

Vitamin D deficiency and insufficiency in patients with chronic kidney disease

Insuficiência e deficiência de vitamina D em pacientes portadores de doença renal crônica

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ABSTRACT

Introduction: Vitamin D deficiency is common among patients with chronic kidney disease (CKD). A higher level of serum vitamin D is expected in residents of the tropics in relation to inhabitants of non-tropical regions, due to greater sun exposure and increased production of vitamin D. **Objective:** To analyze serum levels of vitamin D, such as 25-hydroxyvitamin D – 25(OH)D, in Brazilian patients at the predialytic stage with CKD. **Methods:** We studied 125 patients (aged 57.4 ± 16.2 years, 78 were white and 55.2%, male), with creatinine 2.67 ± 1.73 mg/dL and creatinine clearance 43.7 ± 34.5 mL/min. Body mass index was 27.4 ± 4.7 kg/m², and waist circumference was 95.0 ± 14.0 cm. Calcium was 9.3 ± 0.6 mg/dL, intact parathormone (iPTH) 212.6 ± 221.2 pg/mL and serum albumin 4.2 ± 0.6 g/dL. The mean 25(OH)D was 23.9 ± 10.7 ng/mL. **Results:** Out of the 125 patients, we found that 92 (72.6%) had suboptimal levels of 25(OH)D < 30 ng/mL, and 65 (52%) had vitamin D insufficiency (15–29 ng/mL); 27 (21.5%) had deficiency (5–14 ng/mL) and only one patient had severe vitamin D deficiency < 5 ng/mL. No differences were observed among the levels of 25(OH)D in stratified patients as to the CKD stage. Levels of 25(OH)D were higher among males (38.1 ± 20.6 versus 22.4 ± 9.7 ng/mL; $p < 0.0001$), and there was an inverse correlation between levels 25(OH)D and iPTH, proteinuria and abdominal circumference, and a positive correlation between 25(OH)D and calcium and serum albumin. Multivariate analysis only showed inverse correlation between serum 25(OH)D and iPTH and abdominal circumference. **Conclusion:**

RESUMO

Introdução: Hipovitaminose D é bem documentada em pacientes portadores de doença renal crônica (DRC). Espera-se níveis inferiores em habitantes de regiões não tropicais em relação aos habitantes de regiões tropicais, pela interferência de uma maior exposição solar e maior produção de vitamina D. **Objetivo:** Analisar os níveis séricos de vitamina D, como 25-hidroxivitamina D – 25(OH)D, de 125 pacientes brasileiros portadores de DRC em fase pré-dialítica. **Métodos:** Foram estudados 125 pacientes ($57,4 \pm 16,2$ anos, 78 brancos e 55,2% homens), com creatinina de $2,67 \pm 1,73$ mg/dL e o clearance estimado $43,7 \pm 34,5$ mL/min. O índice de massa corporal era de $27,4 \pm 4,7$ kg/m² e a circunferência abdominal de $95,0 \pm 14,0$ cm. O cálcio era de $9,3 \pm 0,6$ mg/dL, o paratormônio intacto (PTHi) $212,6 \pm 221,2$ pg/mL e a albumina sérica $4,2 \pm 0,6$ g/dL. A média de 25(OH)D era de $23,9 \pm 10,7$ ng/mL. **Resultados:** Dos 125 pacientes, 92 (72,6%) apresentavam níveis de 25(OH)D < 30 ng/mL, sendo que 65 (52%) apresentavam insuficiência (15–29 ng/mL); 27 (21,5%) apresentavam deficiência (5–14 ng/mL) e apenas um paciente apresentava deficiência severa < 5 ng/mL. Não foram observadas diferenças entre os níveis de 25(OH)D nos pacientes estratificados quanto ao estágio de DRC. Os níveis de 25(OH)D foram maiores nos homens ($38,1 \pm 20,6$ versus $22,4 \pm 9,7$ ng/mL; $p < 0,0001$), havendo também uma correlação inversa entre os níveis de 25(OH)D e de PTHi, proteinúria e circunferência abdominal, e uma correlação positiva entre 25(OH)D e cálcio total e albumina sérica. Na análise multivariada, encontrou-se apenas correlação inversa entre 25(OH)D e circunferência abdominal e

Even though the Brazilian population live in a tropical region, most patients had suboptimal levels of serum vitamin D, and this pattern may play a role in the development of hyperparathyroidism.

Keywords: Vitamin D. Vitamin D deficiency. Renal insufficiency, chronic. Nutrition assessment.

PTHi. Conclusão: A despeito de a população do Brasil estar em um clima tropical, a maioria dos pacientes analisados apresentou níveis séricos subótimos de vitamina D, podendo este achado estar relacionado ao desenvolvimento de hiperparatireoidismo.

Palavras-chave: Vitamina D. Deficiência de vitamina D. Insuficiência renal crônica. Avaliação nutricional.

INTRODUCTION

Chronic kidney disease (CKD) is identified as a risk factor for vitamin D deficiency, and many papers show that the frequency of deficiency is high among these patients.¹⁻⁷ Even though little attention has been given to this association up until recently,^{8,9} vitamin D deficiency is not only associated with the increased risk of osteometabolic disease, but also to other relevant clinical issues, including different types of neoplasms,³⁻⁵ besides the risk of cardiovascular diseases.¹⁰ At the same time, low levels of vitamin D have been associated with the high mortality rates in the general population and in patients who undergo hemodialysis (HD).¹¹

The serum concentration of 25-hydroxyvitamin D – 25(OH)D is the main circulating form of vitamin D, used to determine the body standard of vitamin D. It is little studied in regions where solar radiation is considered sufficient, and little is known about the magnitude of vitamin D deficiency in Brazil, be it in the general population or among those who have CKD.^{12,13} Even if Brazil is considered to be an adequate country concerning exposure to the sun, a high percentage of vitamin D deficiency has been reported among people who live in São Paulo.¹³

The objective of this study was to study the frequency of vitamin D deficiency among patients who have CKD undergoing conservative non-dialytic treatment, followed-up at a university reference center.

SAMPLE AND METHODS

Serum levels of 25(OH)D were analyzed in 25 patients who have pre-dialytic CKD; they were aged more than 18 years, being clinically stable and followed-up at the uremia outpatient clinic from 2008-2009. A cross-sectional analysis of serum levels of 25(OH)D and the correlation with anthropometrical (height, weight, abdominal circumference and waist) and lab data [creatinine, alkaline phosphatase, gamma-glutamyltransferase (gamma-GT), total and ionic calcium, phosphorus, albumin, intact parathormone (iPTH) and proteinuria] were performed.

CKD was defined as the estimated creatinine clearance (CrC) < 90 mL/min and signs of renal lesion.^{14,15} Patients were stratified in four stages of CKD, according to the guidelines of the Brazilian Society of Nephrology:¹⁵ stage 2 – slight or functional CKD (CrC from 60–89 mL/min); stage 3 – moderate or lab CKD (CrC from 30–59 mL/min); stage 4 – severe or clinical CKD (CrC from 15–29 mL/min); and stage 5 – pre-dialytic CKD (CrC < 15 mL/min).

None of the patients was on vitamin D supplementation, and the confirmed diagnosis of CKD was the only indication for the dosage of serum 25(OH)D; the patient should also be included in a research protocol previously approved by the Research Ethics Committee of the institution.

Blood samples were drawn for lab tests after an eight-hour fast, and included the blood dosage of: creatinine, urea, calcium – reference value (RV) (= 8.5 to 10.5 mg/dL), phosphorus (RV = 2.3 to 4.6 mg/dL), alkaline phosphatase (RV = 40 to 104 U/L), bicarbonate, albumin and iPTH (RF = 11 to 62 pg/mL). Biochemical dosages were performed by the automated method (*Autoanalyzer*, EUA). Serum iPTH was measured by the immunoradiometric methods (IRMA). Serum creatinine was measured by the automated method, by Jaffe reaction, and the renal function was evaluated by creatinine clearance (CrC; in mL/min) estimated by the Cockcroft-Gault equation:¹⁶ {CrC = [(140-age) x weight]/(72 x Cr)}, multiplied by 0.85 for women, since age is measured in years; weight, in kilograms; and serum creatinine (Cr), in mg/dL. Total serum calcium was corrected by the concentration of serum albumin with the equation:¹⁷ $Cac = Ca + [0.8 \times (4.5 - Alb)]$. All dosages were performed at the Central Laboratory of the Hospital. The dosage of serum concentration of 25(OH)D was performed by the Diasorin Liaisontm method (USA), based on chemiluminescence to recognize vitamin D-binding proteins. Vitamin D deficiency and insufficiency were defined according to the guidelines proposed by the Kidney Disease: Improving Global Outcomes (KDIGO).¹⁸ Thus, serum levels of vitamin D were considered as adequate when the concentration of 25(OH)D was

higher than 30 ng/mL; levels between 16-30 ng/mL were considered as insufficient, and values that were equal or lower than 15 ng/mL defined the diagnosis of vitamin D deficiency.

STATISTICAL ANALYSIS

Characteristics of patients were summarized by frequency, for categorical variables, and by central tendency for continuous variables (mean \pm standard deviation). Continuous variables were tested as to normal distribution with the Kolmogorov-Smirnov test, and the differences were analyzed by the Mann-Whitney test. In order to analyze CKD stages, the one-way (ANOVA) technique was used. Meanwhile, the linear correlation analysis was used to determine the relations between continuous variables (Pearson's or Spearman's coefficient, when indicated). The univariate analysis was used to correlate serum levels of 25(OH)D and the clinical and biochemical parameters studied with the multiple linear regression analysis (stepwise) to check for independent predictors of the concentration of 25(OH)D. Variables that presented significant correlations in the univariate analysis were included in the model. Differences with $p < 0.05$ were considered significant. The software SPSS for Windows (Inc., Chicago, III, USA) was used for analysis.

RESULTS

BASAL CHARACTERISTICS OF THE PATIENTS

The characteristics of the studied patients are demonstrated in Table 1. Out of the 125 analyzed patients, 69 (55.2%) were males, with mean age of 57.4 ± 16.2 years (ranging from 18-85 years). Seventy eight were white. The most common primary renal disease was hypertensive nephroangiosclerosis (in 45 patients) and diabetic nephropathy (in 32 patients). No patient presented with severe liver injury, congestive heart failure or malignant neoplasm. Mean weight of the patients was 72.1 ± 15.8 kg, body mass index (BMI) was 27.4 ± 4.7 kg/m² (variation: 17.4–42.4 kg/m²), mean waist was 95.0 ± 14.1 cm. The analyzed biochemical variables are also demonstrated in Table 1. Serum creatinine was 2.66 ± 1.74 mg/dL, and the estimated creatinine clearance was 43.7 ± 34.5 mL/min (variation: 8.7–89.3 mL/min).

VITAMIN D STANDARD AMONG PATIENTS

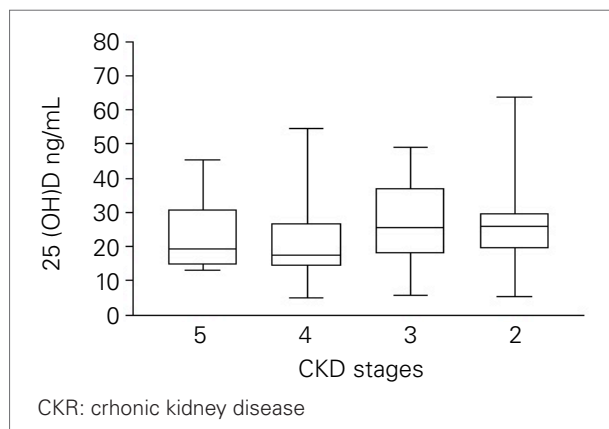
Out of the 125 analyzed patients, 92 (73.6%) had low levels of serum 25(OH), that is, serum concentration was ≤ 30 ng/mL; out of these, 65 (52.0%) had

Table 1 CLINICAL AND LABORATORY DATA OF THE 125 STUDIED PATIENTS

Patients	125
Age (years)	57.4 ± 16.3
Males	69 (55%)
Weight (kg)	72.1 ± 15.8
BMI (kg/m ²)	27.4 ± 4.7
Waist (cm)	95 ± 14
Hip (cm)	103 ± 11
Waist/hip index	0.92 ± 0.09
Men	0.97 ± 0.06
Women	0.87 ± 0.09
Creatinine clearance (mL/min)	43.7 ± 34.5
Creatinine (mg/dL)	2.66 ± 1.74
Calcium (mg/dL)	9.3 ± 0.6
Ionic calcium (mg/dL)	5.1 ± 0.4
Phosphorus (mg/dL)	3.9 ± 0.8
iPTH	212.6 ± 221.2
Alkaline phosphatase (UI)	94.1 ± 34.6
Gamma-glutamyltransferase	52.0 ± 66.2
Albumin	4.2 ± 0.6
24h proteinuria	1.12 ± 2.27

BMI: body mass index; iPTH: intact parathormone.

Figure 1. Values of 25(OH)D in relation to the renal function, stratified according to CKD staging (ANOVA: $p = 0.1258$).



insufficient levels of vitamin D, and the 27 others (21.6%) had levels lower than 15 ng/mL, considered as deficient. Only one patient presented less than 5 ng/mL, which is considered as severe insufficiency. No differences were observed between levels of 25(OH)D in patients stratified as to CKD stage ($p = 0.1258$) – Figure 1. In the univariate analysis, no correlation between serum levels of 25(OH)D and the estimated creatinine clearance of patients ($r = 0.03346$; $p = 0.7122$) was observed – Figure 2. Likewise, the age, height, weight, ionic calcium, phosphorus, creatinine,

alkaline phosphatase and gamma-GT of the patients were not correlated. Serum levels of 25(OH)D were higher for males (38.1 ± 20.6 ng/mL *versus* 22.4 ± 9.7 ng/mL; $t = 5.377$, $p < 0.0001$).

Serum concentrations of iPTH ranged from 23–1.076 pg/mL, and a significant negative correlation was noticed between 25(OH)D and serum iPTH ($r = -0.317$, $p = 0.013$) – Figure 3, the waist circumference of patients ($r = -0.189$, $p = 0.045$) and 24-hour proteinuria ($r = -0.315$, $p = 0.0063$). Levels of 25(OH)D were also significantly correlated with the concentrations of total serum calcium ($r = -0.2110$, $p = 0.04$) and serum albumin ($r = 0.2601$, $p = 0.03$). At the multivariate analysis, independent predictors of levels of 25(OH)D were waist circumference [coefficient = -0.1515 , standard error (SE) = 0.07566 , $r = -2.002$, $p = 0.0332$] and iPTH concentrations (coefficient = -0.01168 , SE = 0.004551 , $r = -2.567$, $p = 0.0063$).

Figure 2. Values of 25(OH)D in relation to the renal function: (A) normal levels; (B) insufficient levels and (C), levels of vitamin D deficiency ($r = 0.048$; $p = 0.6017$).

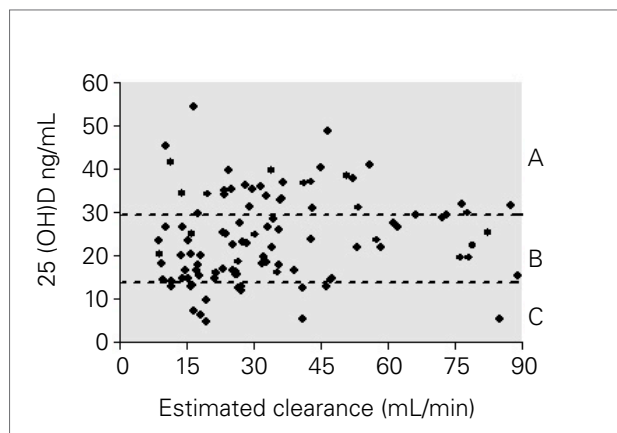
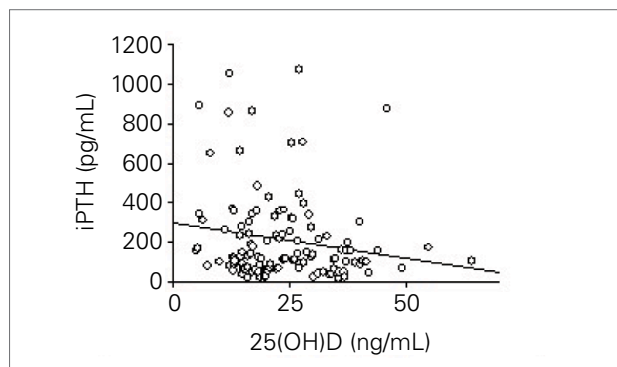


Figure 3. Correlation between serum levels of 25(OH)D and serum concentrations of iPTH of the studied patients ($r = -0.3179$; $p = 0.0130$).



DISCUSSION

This study showed a high prevalence of vitamin D deficiency/insufficiency in patients with pre-dialytic CKD, and this condition is observed in 72.6% of the studied patients. Besides, low values of 25(OH)D were associated with high levels of iPTH and abdominal circumference of patients. These data suggest an important role of the suboptimal levels of vitamin D in the physiopathogeny of hyperparathyroidism in patients with CKD.

The presence of vitamin D deficiency in the general population and in patients with CKD has been described. It is estimated that about 1 million people all over the world have vitamin D deficiency¹¹, and the extensive 2007 North-American study, NHANES, showed a significant deficiency of 25(OH)D₃ in patients with stage 4 CKD.¹⁹ Concerning those who do not have CKD, data on blood levels of vitamin D are scarce, being almost exclusively described in small groups of individuals such as children, adolescents and the elderly.

This clinical problem has always been seen as something small in our country, since most of its territory is located in a tropical region, where the incidence of sun light is excessive. However, such premise has been refuted by studies that prove the high frequency of vitamin D deficiency in the Brazilian population^{13,20-22}. A study that included 250 elderly people living in São Paulo demonstrated a high and unexpected prevalence of vitamin D deficiency (15.4%) and insufficiency (41.9%).²¹ Also in relation to Brazilian data, a study was performed with 16 healthy teenagers from the countryside of São Paulo and showed high prevalence (60%) of vitamin D insufficiency.²² A study involving 603 normal volunteers, also from São Paulo, found mean value of 25(OH)D of 21.4 ng/mL, and 77.4% of the analyzed patients had vitamin D deficiency.¹³ Vitamin D deficiency was more common among black people and the elderly population; it was associated to higher blood levels of PTH and was more common during the winter.

In relation to patients with non-dialytic CKD, data in this study showed the high prevalence of vitamin D deficiency and insufficiency, according to literature.^{1,2} Observations have shown that CKD is associated with the high incidence of vitamin D deficiency.²³ A study performed in 2004 with limited number of patients with CKD also showed that vitamin D insufficiency and deficiency were prevalent among patients with CKD, affecting

86% of the patients, and that the functional meaning of this finding is yet to be determined.¹ In another analysis involving 76 Japanese patients with CKD, serum levels of 25(OH)D were associated with hypoalbuminemia, diabetes mellitus and serum phosphorus, but no correlation was found between serum levels of 25(OH)D and creatinine clearance of the patients.² In these studies, 25(OH)D insufficiency and deficiency have also been associated with the presence of hyperparathyroidism during CKD, which leads to the evaluation of the levels of this vitamin in patients with CKD and hyperparathyroidism; if the value of 25(OH)D is lower than 30 ng/mL, it is replaced.

Reasons for the high frequency of vitamin D deficiency in patients with CKD are not clear, although it has been described that renal dysfunction is a risk factor for vitamin D deficiency.^{24,25} Likewise, it is a known fact that the presence of nephrotic proteinuria is associated with vitamin D deficiency, possibly due to the urinary loss of vitamin D bound to its plasma carrier protein.²⁶ As to the patients analyzed in this study, those who had the nephrotic syndrome presented serum levels of 25(OH)D \leq 30 ng/mL. However, this factor should not be the only one, since many patients who did not have nephrotic proteinuria also presented with vitamin D deficiency.²⁴ However, it is important to observe that the high frequency of vitamin D deficiency in our sample of patients with CKD (73.6%) is not different from that recently demonstrated in healthy people living in São Paulo, in which 77.4% of the people presented serum levels of 25(OH)D < 30 ng/mL.¹³

The consequences of vitamin D deficiency in patients with CKD are not established yet. This item is especially important due to the observation that administering active vitamin D in patients with dialytic CKD was associated with better survival rates, when compared to patients who did not use any vitamin D analogues.^{27,28} An analysis with 444 patients followed-up for about 9.4 years – 51.1% of mortality – showed that reduced levels of 25(OH)D were associated with mortality due to all causes and cardiovascular motives.²⁹

Therapy with ergocalciferol or colecalciferol in patients with CKD with 25(OH)D deficiency has been little described in literature, thus showing it is associated with high serum levels of this vitamin for most patients, and with the reduction of PTH levels among those who respond to treatment.^{26-28,30-32} However, the possible advantages of this supplementation are yet to be defined. Evidence shows that pleiotropic effects of

vitamin D go beyond bone and mineral metabolism and the activity of parathyroid glands, thus being possibly related to other potential areas of CKD. It has been demonstrated that vitamin D supplementation has an antiproteinuric effect,³³ to regulate the renin-angiotensin-aldosterone,³⁴ to reduce histological changes found in glomerulosclerosis,³⁵ and, finally, to reduce CKD progression.⁴

To sum up even if our population with CKD is in a tropical environment, which leads to more exposure to the sun and, consequently, a higher production and serum levels of 25(OH)D, our study showed that most analyzed patients had serum levels of 25(OH)D below recommended values, especially lower among women and in patients with larger abdominal circumference. These suboptimal serum levels of vitamin D can be related to the appearance of hyperparathyroidism.

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