

Serum levels of vitamin D and chronic periodontitis in patients with chronic kidney disease

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ABSTRACT

Introduction: Concomitance of chronic periodontitis (CP) in patients with chronic kidney disease (CKD) have been associated with adverse outcomes. Vitamin D (25(OH)D) deficiency may play a role in CP and inadequate vitamin D status is common among patients with CKD. **Objective:** To examine the relationship between vitamin 25(OH) D and CP in patients with CKD not yet on dialysis. **Methods:** A case-control study was conducted. Cases and controls were defined as patients with CKD with and without CP, respectively. The demographic, clinical and laboratory data were obtained when the patient was attended in the outpatient clinic. CKD was defined and staged according to the NKF QDOKI™. Serum 25(OH)D levels were measured by chemiluminescence when assessing the CP, which was defined according to the American Academy of Periodontology (1999). Serum 25(OH)D levels were stratified into deficient (≤ 14 ng/mL), insufficient (15-29 ng/mL) and sufficiency (≥ 30 ng/mL). **Results:** A total of 15 cases were compared with 14 controls. Cases had lower median 25(OH) D levels than controls (22.6 *versus* 28.6 ng/mL, $p < 0.01$) and were more likely to be categorized as vitamin D insufficiency/deficiency (93,3% *versus* 57,1%, $p < 0,004$). On the other hand, the percentage of controls with vitamin D sufficiency was higher than cases (42,9% *versus* 6,7%, $p < 0,004$). **Conclusion:** In patients with CKD not yet on dialysis, vitamin D deficiency is associated with CP.

Keywords: chronic periodontitis, renal insufficiency, chronic, vitamin D.

INTRODUCTION

Chronic periodontitis (CP) is a subgingival infection predominantly caused by gram-negative¹ bacteria and is characterized by periods of exacerbation and remission. In Brazil, about 70% of persons over the age of 30 years have moderate CP, represented by a clinical attachment level (CAL) of ≥ 5 mm, and 52% have the severe form of the disease (CAL ≥ 7 mm).² Patients undergoing predialysis and hemodialysis showed a prevalence of more severe CP when compared with peritoneal dialysis patients and healthy persons.³ CP in its severe form can lead to dental loss⁴ and is associated with increased risks of cardiovascular disease,⁵ inadequate glycemic control in patients with type 2 diabetes mellitus,⁶ complicated pregnancy,⁷ and stroke,⁸ and is considered a major public health problem that can be prevented and treated.

Recent studies suggest a high prevalence of CP in patients with chronic kidney disease (CKD), both in the predialytic^{9,10} and dialytic stages.^{11,12} In patients with CKD, CP is more serious and there is a higher prevalence of periodontal bacterial pathogens compared with healthy persons.¹³ The unfavorable impact of the occurrence of CP in the course of CKD is not fully defined; however, its unfavorable association with cardiovascular diseases,¹⁴ a leading cause of death in patients with kidney disease,¹⁵ may constitute a new, as of yet undervalued risk factor.

Vitamin D plays an important role in the immune response and may play a key role in CP observed in patients with CKD. Studies have reported an association between periodontal health and intake of vitamin D.^{16,17} Vitamin D and calcium supplements improve periodontal health, increase bone density in the jaw bone, and inhibit alveolar bone resorption.^{18,19} We postulate that an inadequate level of vitamin D promotes the occurrence of CP in patients with CKD; therefore, the objective of this study was to examine the relation between serum vitamin D levels and CP in patients with predialysis CKD.

METHODS

This was a case-control study of patients treated at the secondary prevention outpatient unit of the Nucleus of Interdisciplinary Studies, Research and Treatment of Nephrology (NIEPEN), Federal University of Juiz de Fora and IMEPEN Foundation, from 11/2009 to 08/2012.

Patients of both sexes and with predialysis CKD stages 3B to 5, in the 30-78 years age group, were included. Patients who were smokers, those using anti-inflammatory drugs, those using antibiotics in the last 3 months, pregnant women, cancer patients, HIV patients, uncompensated diabetics, patients with other infections or fever of undetermined origin, those treated for periodontitis in the last 6 months, and those with aggressive or acute periodontal disease were excluded.

The glomerular filtration rate (GFR) was estimated on the basis of the concentration of serum creatinine, using the equation developed by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) study group.²⁰ The diagnosis of CKD followed the criteria proposed by the NKF KDOQI™ (National Kidney Foundation/Kidney Disease Outcomes Quality Initiative).²¹

The level of 25-hydroxyvitamin D, 25(OH)D, was assessed by a chemiluminescence analysis of serum stored at -80°C, obtained on the day of periodontal examination. The serum levels of 25(OH)D were used as organic reserves of vitamin D. The serum 25(OH)D level is the combination of endogenous and exogenous sources of vitamin D and presents prolonged half-life.²² 25(OH)D levels were stratified into deficiency (≤ 14 ng/mL), insufficiency (15-29 ng/mL), and sufficiency (≥ 30 ng/mL).

Periodontal examination was conducted by 2 suitably qualified examiners. All teeth, except the third molars, were examined. Probing depth (PD) and gingival recession were measured at 6 sites per tooth (mesio-buccal, buccal, disto-buccal, mesio-lingual, lingual, disto-lingual) by using an electronic probe (Florida Probe Corp., USA). The measurements were expressed in millimeters. The CAL was calculated using the distance of the PD from the cementum/enamel junction, added to gum recession, and subtracting gingival hyperplasia. The number of sites with plaque was quantified by the presence or absence of supragingival dental plaque as well as the number of sites with bleeding on probing.

The professional skill was tested by the correlation coefficient, using the κ -test. The intra-examiner coefficient was 0.84 and the inter-examiner coefficient was 0.82.

The project was approved by the Ethics in Research Committee (CEP-HU/CAS) of the Federal University of Juiz de Fora, Opinion N° 0130/2009; cover page: 290100; CAAE: 0107.0.420.000-09.

STATISTICS

Data were collected and processed using SPSS, version 15.0 (Chicago, IL, USA). The results were presented as medians and values (minimum and maximum) for numeric variables, and absolute and relative frequencies for categorical variables. To compare the variables between groups, the Mann-Whitney test for numerical variables and the χ^2 or Fisher exact test (when the expected frequencies were < 5) for categorical variables were applied. Statistical difference was considered for p values < 0.05 .

RESULTS

Of the 623 patients initially assessed, 594 were excluded for the following reasons: a GFR of > 44 mL/mi/1.73 m² (252), nonattendance to periodontal evaluation and blood collection (139), total edentulism (108), smoking (48), refusal to participate in the study (31), and no indication of periodontal evaluation (16). Twenty-nine patients met the inclusion criteria, 15 in the case group (CKD and CP) and 14 in the control group (CKD without

CP), with a similar median age in both groups. The case group, compared with the control group, was composed primarily of male patients and diabetics; however, the differences were not statistically significant (Table 1). The most common causes of CKD were diabetic renal disease in patients in the case group and hypertensive nephropathy and diabetic kidney disease in the control group. There was a statistical difference in the median systolic blood pressure (140 mmHg *vs.* 130 mmHg, $p < 0.05$) and parathyroid hormone levels (105 pg/mL *vs.* 53 pg/mL, $p < 0.05$), both being higher in case patients than in control patients.

As expected, a statistical difference was observed in all clinical periodontal parameters in the comparison groups. Case patients had higher local inflammation and CP characterized as moderate to severe, with involvement of many sites of the mouth (PD ≥ 5 mm = 5.5% and CAL ≥ 6 mm = 32%, $p < 0.001$). There was no statistical significance in the number of teeth (Table 2).

Case patients had a lower median level of 25(OH)D than control patients (22.6 *vs.* 28.6 ng/mL, $p < 0.01$) (Figure 1). The percentage of CKD patients with and without CP in accordance with the levels of 25(OH)D was 33.3% *vs.* 0% in the deficiency group, 60% *vs.* 57.1% in the insufficiency group, and 6.7% *vs.* 42.9% in the sufficiency group ($p < 0.004$). The percentage of patients with insufficiency or deficiency of 25(OH)D was significantly greater among case patients than among control patients (93.3% *vs.* 57.1%, $p < 0.004$).

DISCUSSION

This study shows that patients with CKD and CP have lower serum levels of vitamin D and are most often insufficient and deficient in 25(OH)D in relation to CKD patients without CP. This association was evident despite excluding several confounding factors such as smoking, use of anti-inflammatory medications, recent antibiotic use, pregnancy, cancer, infection with human

TABLE 1 DEMOGRAPHIC, CLINICAL, AND LABORATORY DATA OF CHRONIC KIDNEY DISEASE (CKD) PATIENTS WITH AND WITHOUT CHRONIC PERIODONTITIS (CP)

Variables	CKD with CP (n =15), median (min-max)	CKD without CP (n = 14), median (min-max)	p-value
Age, years	63 (51-72)	64 (30-78)	0.5
Sex (male), %	67	50	0.2
Diabetes, %	46	21	0.1
Hypertension, %	86	93	0.5
Basal disease			0.5
Hypertensive nephropathy, %	20	21.4	
Diabetic nephropathy, %	40	21.5	
Chronic glomerulonephritis, %	6.7	14.3	
Other and unspecified, %	33.3	42.8	
Systolic blood pressure, (mmHg)	140 (100-190)	130 (100-180)	0.014
Diastolic blood pressure, (mmHg)	80 (60-100)	80 (68-130)	0.6
Body mass index, (kg/m ²)	27 (17-39)	26 (21-86)	0.8
Serum creatinine, (mg/dL)	1.8 (1.3-5)	1.7 (0.8-3.2)	0.2
GFR, mL/min/1.73 m ²	31 (9-63)	32 (15-78)	0.3
Total cholesterol, (mg/dL)	183 (109-330)	192 (119-255)	0.4
Parathyroid hormone, (pg/mL)	105 (39-595)	53 (22-175)	0.02
Distribution of patients according to 25(OH)D levels, n (%)			0.004
≤ 14 ng/mL	5 (33.3)	0	
15-29 ng/mL	9 (60)	8 (57.1)	
≥ 30 ng/mL	1 (6.7)	6 (42.9)	

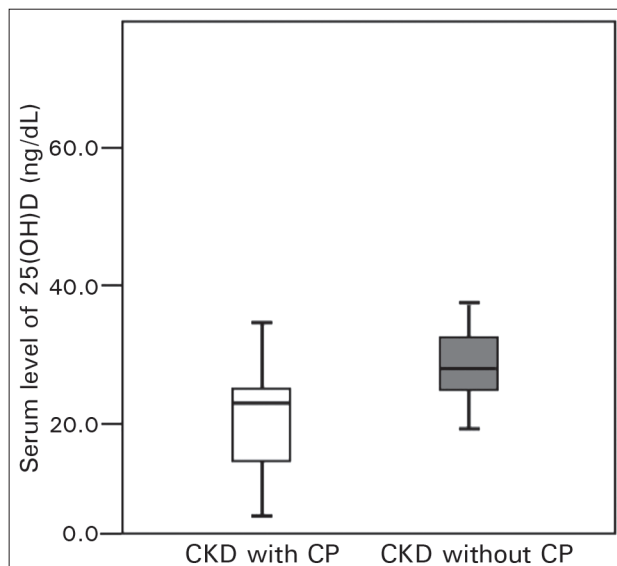
GFR: Glomerular filtration rate; 25(OH)D, 25-hydroxy vitamin D.

TABLE 2 EVALUATION OF CLINICAL PERIODONTAL PARAMETERS IN CHRONIC KIDNEY DISEASE (CKD) PATIENTS WITH AND WITHOUT CHRONIC PERIODONTITIS (CP)

Variables	CKD with CP (n =15), median (min-max)	CKD without CP (n = 14), median (min-max)	p-value
Probing depth, mm	2.1 (1.4-3.7)	1.4 (1.3-1.8)	< 0.001
Probing depth ≥ 5 mm, %	5.5 (2-36)	*	
Clinical attachment level, (mm)	4.5 (1.7-6)	2.2 (1.4-4.9)	< 0.001
Clinical attachment level ≥ 6 mm, %	32 (2.7-54)	*	
Sites with dental plaque, %	85 (2-100)	3.5	< 0.001
Sites with bleeding on probing, %	52 (2-98)	*	
No. of teeth	14 (4-23)	12 (6-26)	0.9

* Unique and defining factors of the case group for the clinical confirmation of CP; not observed in the control group.

Figure 1. Box-plot representing the median (horizontal line), interquartile range (upper and lower), and upper and lower limits (rods) of 25(OH)D levels in patients with chronic kidney disease (CKD) and chronic periodontitis (CP) (case patients) compared with those with CKD without CP (control patients). Case patients had a lower median serum level of 25(OH)D than control patients ($p < 0.01$).



immunodeficiency virus, uncompensated diabetes, fever of unknown origin or other infections, periodontal treatment within the last 6 months, and cases of aggressive or acute periodontal disease. The results suggest that a sufficient level of vitamin D is important in maintaining a healthy periodontium and reducing the consequences of CP.

Vitamin D deficiency is not uncommon in Brazil. Among the 73 resident physicians of a public hospital in the city of Porto Alegre, with a mean age of 26 years, the serum level of 25(OH)D found was 17.9 ± 8.0 ng/mL, and in 57.4% of them, vitamin D levels were < 20 ng/mL.²³ In CKD, insufficient

levels of 25(OH)D, defined as < 30 ng/mL, were observed in 39.6% of patients undergoing conservative treatment in São Paulo.²⁴ However, if we consider 25(OH)D levels ≥ 40 ng/mL^{25,26} as sufficient, the percentage of insufficient patients reaches 51%.²⁷ In this study, 75.8% of CKD patients evaluated had insufficient or deficient levels of vitamin D and, of these, 63.6% had CP.

CP is a chronic infectious disease caused by gram-negative bacteria, which induces a systemic inflammatory response.⁴ The destruction of local periodontal tissue promotes systemic dissemination of periodontal pathogens and their products (e.g., lipopolysaccharides) and of inflammatory mediators (e.g., tumor necrosis factor, interleukin-6) produced locally.²⁸ In previous studies, CP tended to be more severe in patients with CKD undergoing dialysis or conservative treatment, compared with patients with CP and without systemic diseases.^{13,29} In this study, the CP was very well defined in case patients, with all clinical parameters used for characterizing periodontal disease being statistically different from control patients.

In NHANES III (third National Health and Nutritional Examination Survey), a significant survey of the adult population of the United States of America, insufficient levels of 25(OH)D were associated independently with CP.¹⁶ In a randomized trial, the administration of vitamin D (700 IU/day) and calcium (500 mg/day) significantly reduced tooth loss in older patients during 3 years of observation.³⁰ In addition, dietary supplementation with vitamin D and calcium improved periodontal health, increased jaw bone density, inhibited bone resorption,^{18,19} and decreased the severity of CP.³¹

Vitamin D has important functions in immune and inflammatory responses and, when lacking, is associated with a higher prevalence of infection.³² Vitamin D acts as an anti-inflammatory agent by inhibiting the expression of inflammatory cytokines and stimulating monocytes/macrophages to secrete molecules with potent antibiotic effects.^{16,17} Vitamin D directly induces the expression of the endogenous antimicrobial peptide cathelicidin, the production of which is triggered by Toll-like receptors in response to bacterial infection. Activation of Toll-like receptors in human macrophages increases the expression of vitamin D receptors and the enzyme α -1-hydroxylase. Consequently, there is an induction of cathelicidin and an intracellular killing of bacteria (e.g., *Mycobacterium tuberculosis*).³³ CP is caused by bacteria that stimulate the immune and inflammatory responses as part of the organism's defense mechanisms, and responses through Toll-like receptors are important in the pathogenesis of periodontal disease.^{34,35} Vitamin D appears to modulate most of the host's immune response.³⁶ In our study, patients with CKD and CP had lower levels of 25(OH)D than control patients without CP. We also observed that CP occurred more often in patients with < 30 ng/mL 25(OH)D, one-third of whom were deficient in vitamin D. Moreover, only 6.7% of patients with CKD and CP showed sufficient levels of 25(OH)D.

In this study, our concern in the pairing of case and control patients as much as possible was evident. We matched patients according to several traditional confounding factors that are associated with CP, such as age, sex, obesity, and smoking. However, there was a statistical difference between the levels of systolic blood pressure, which was higher in patients with CP. Current epidemiological evidence reinforces the association of CP with high blood pressure. The mechanisms involved in this association appear to involve the systemic dissemination of periodontal infection, host immune response, direct bacterial action on the vascular system, endothelial dysfunction³⁷ and/or hyperparathyroidism,³⁸ and/or inadequate regulation of the renin-angiotensin system by vitamin D.³⁹

It is known that vitamin D deficiency occurs early in the course of CKD⁴⁰ and is associated with

secondary hyperparathyroidism.⁴¹ These observations are consistent with our findings of higher levels of intact parathyroid hormone in patients with CKD and CP, who are relatively more deficient in vitamin D than those with a healthy periodontium.

It is imperative to present some limitations of our work. First, the cross-sectional nature of this study does not allow us to establish a causative association between vitamin D deficiency and CP. Second, the strict inclusion and non-inclusion criteria limited the sample size. Third, the use of 30 ng/mL as a cutoff point for establishing the organic reserves of 25(OH)D may be debatable since some authors recommend levels of 40 ng/mL or more as optimal.^{25,26} Finally, it is possible that there are other confounding factors that might explain our results.

In summary, our findings suggest that vitamin D deficiency predisposes patients with CKD to develop CP, possibly by limiting the patient's inflammatory and immune response against bacterial invasion of the periodontium.

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