High prevalence of vitamin D deficiency among children with chronic kidney disease and kidney transplant

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ABSTRACT

Introduction. Vitamin D (25(OH)D) deficiency is common among patients with chronic kidney disease (CKD). Our objective was to establish the prevalence of 25(OH)D deficiency among children with CKD and identify risk factors. A correlation was observed between 25(OH)D and parathormone intact molecule.

Population and methods. Cross-sectional study conducted between January 2013 and December 2015. Patients younger than 19 years old with and without CKD were included.

Results. One hundred and sixty-seven patients were included. Group 1 (healthy controls): 32 participants; group 2 (stage 2-4 CKD, glomerular filtration rate between 89 and 15 mL/min/1.73 m^2): 34 patients; group 3 (stage 5 CKD, dialysis): 46 patients; and group 4 (kidney transplant recipients): 55 patients.

Deficiency of 25(OH)D was detected in 12.5% of healthy controls and 32% of CKD patients (p= 0.025).

Also, 23% of patients in group 2, 51% in group 3, and 22% in group 4 had 25(OH)D deficiency; the mean 25(OH)D level of dialysis patients was significantly lower than that of the rest of the groups. Predictors of 25(OH)D deficiency included hypoalbuminemia, advanced CKD, and place of origin from the Northwest region of Argentina. The parathormone intact molecule was significantly higher in the group of patients with deficiency and was inversely correlated with 25(OH)D levels.

Conclusion. Among CKD patients, 32% had 25(OH)D deficiency, which reached 51% among those with stage 5 CKD (dialysis). Predictors of deficiency included hypoalbuminemia, advanced CKD, and place of origin from the Northwest region of Argentina.

Key words: *vitamin D deficiency, chronic kidney disease, dialysis, hyperparathyroidism.*

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INTRODUCTION

Vitamin D deficiency is very common among patients with chronic kidney disease (CKD).[1-3] Vitamin D is mainly involved in phosphocalcic metabolism regulation, but it also plays an important role in the prevention of cardiovascular risk, infectious and autoimmune diseases, and CKD progression.[2,4,5]

Undoubtedly, factors determining such cardiovascular and bone risk increase are present in the pre-dialysis period and further increase during renal replacement therapy with dialysis or a kidney transplant.[4,6-9]

Some studies conducted in children with CKD showed that vitamin D administration reduced proteinuria and kidney disease progression.[5] Treatment with vitamin D in patients with CKD improves their long-term survival and reduces their cardiovascular risk.[10,11]

The circulating level of 25-hydroxy-vitamin D (25(OH)D) is the best marker of a subject's status in terms of vitamin D levels based on its prolonged circulation half-life and the fact that it does not build up in tissues. The measurement of 25(OH)D reflects vitamin D dietary intake, vitamin D produced in the skin from exposure to sunlight, and vitamin D made in the liver from adipose tissue deposits.[3]

However, levels may vary depending on the season, duration of exposure to sunlight, sunscreen use, dietary intake, and urinary loss of vitamin D binding protein.[10,11]

Studies have been conducted worldwide to establish vitamin D deficiency prevalence among children

with CKD. Vitamin D deficiency ranges between 30% and 50% in this population.[11-15] These studies were conducted in Europe and the Unites States of America, but there is scarce information in this regard about Latin America.[16]

The objectives of this study included establishing the prevalence of vitamin D deficiency among children with CKD and identifying associated risk factors and the relationship with parathormone (PTH) intact molecule.

POPULATION AND METHOD

This was an observational, cross-sectional, and analytical study conducted at the Service of Clinical Pediatrics and the Service of Pediatric Nephrology of the Department of Pediatrics of Hospital Italiano de Buenos Aires between January 2013 and December 2015.

The following patients were included: 1) patients aged 1 to 19 years with stage 2-5 CKD, a glomerular filtration rate (GFR) between 0 and 89 mL/min/1.73 m^2; 2) pediatric kidney transplant recipients who had a functioning graft and a GFR higher than 30 mL/min/1.73 m^2, and who had been stable for at least 6 months prior to study enrollment; and 3) children younger than 19 years old seen at the Pediatrics outpatient offices for routine or pre-surgical lab tests (control group).

Children were excluded if they had primary endocrine disorders related to phosphocalcic metabolism, liver failure, digestive tract disorders related to malabsorption, gluten allergy, anticonvulsant use, prolonged high-dose corticosteroid use, and if they had undergone a parathyroidectomy. Kidney transplant recipients were on low-dose corticosteroids as part of their immunosuppressive scheme (0.1-0.3 mg/kg/day).

The protocol implemented in our site is based on a triple immunosuppression scheme made up of methylprednisolone, tacrolimus, and mycophenolate mofetil. Patients who received a graft from a deceased donor underwent induction therapy with thymoglobulin and corticosteroids whereas those who received a graft from a living related donor received corticosteroids and daclizumab or basiliximab.

Dialysis patients had been on stable peritoneal dialysis (PD) or hemodialysis for 3 months.

Study procedures and definitions

Patients who attended our unit over the study period and who met the inclusion criteria were invited to participate in the protocol.

Children without CKD seen at the Department of Pediatrics for routine or pre-surgical lab tests were selected as healthy controls.

Blood 25(OH)D, calcium, phosphor, creatinine, PTH intact molecule, and albumin levels were recorded, in addition to weight and height, to estimate GFR, body mass index (BMI) and height Z-score. Most of the time, determinations were done together with routine lab checkups to prevent any interference with follow-up.

The time of the year for sample collection and the usual medications taken by each patient were recorded. If they received exogenous vitamin D2 or D3, the active ingredient and the dose were recorded to analyze their probable relationship with the studied outcome measures. Many patients were taking multivitamin supplements. For the analysis in relation to vitamin D supplements, only those containing more than 400 IU/day were taken into consideration.

Chronic kidney disease definition

GFR < 90 mL/min/1.73 m^2 for more than 3 months. CKD stages were classified as per the international criteria established by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2012.[17]

Stage 2: GFR 89-60 mL/min/1.73 m^2; stage 3: GFR 59-30 mL/min/1.73 m^2; stage 4: GFR 29-15 mL/min/1.73 m^2; stage 5: GFR < 15 mL/min/1.73 m^2 (requiring renal replacement therapy, dialysis and/or kidney transplant).

GFR was estimated by the "Bedside Schwartz" formula (2009)[18] based on plasma creatinine determined using Jaffe's kinetic method, with traceability adequate for international reference standards and a minimum deviation from the reference isotope dilution mass spectrometry method.

The following PTH intact molecule levels were considered optimal for each stage: stages 2 and 3, 35-70 pg/mL; stage 4, 71-110 pg/mL; stage 5, 200-300 pg/mL.[19,20]

Levels of 25(OH)D were estimated by the radioimmunoassay method.

Based on the 25(OH)D level, the following categories were established: vitamin D deficiency (< 20 ng/mL), and adequate vitamin D level (≥ 20 ng/mL).

The level of 25(OH)D was considered the main outcome measure in the study.

CKD causes were categorized as congenital urinary tract abnormalities (this category included renal hypoplasia or dysplasia,

multicystic dysplastic kidney, and obstructive uropathy), focal segmental glomerulosclerosis (FSGS), hemolytic uremic syndrome (HUS), and other causes (this category included glomerular diseases other than FSGS, polycystic kidney disease, and other less common congenital diseases).

Only 15% of samples were collected during the winter.

Ethical considerations

The study was approved by the Ethics Committee and the Research Committee of our hospital. Patients were included once their parents had signed an informed consent form.

Children's assent for study inclusion was requested if adequate for their age.

Statistical analysis

Sample size estimation: given CKD prevalence among children younger than 19 years old is approximately 60 per one million inhabitants younger than 19, and considering a 95% confidence level and an 80% power, 130 patients had to be included in the study.

Continuous outcome measures were described as median and ranges or mean ± standard deviation (SD) for abnormal or normal distribution, respectively. Categorical outcome measures were stated in percentages and frequencies.

Differences between two groups of CKD patients with and without 25(OH)D deficiency were analyzed using Student's t test for independent samples or the Mann-Whitney U test, as necessary. Differences among the study patient groups were compared using an analysis of variance (ANOVA). Post-test comparisons were done with the Kruskal-Wallis test for non-parametric data. Qualitative outcome measures were analyzed using the χ^2 test or Fisher's test, as applicable.

A logistic regression analysis was done for CKD patients to establish risk factors for 25(OH)D deficiency. The outcome measures included in the model were those with a p value < 0.1 in the univariate analysis.

Analyzed independent outcome measures were as follows: age, sex, PTH intact molecule, albumin, underlying disease, CKD stage, height Z-score, and Argentine region of origin.

The software used for statistical analysis was SPSS Windows (version 22).

A value of $p < 0.05$ was considered significant.

RESULTS

One hundred and sixty-seven patients who agreed to participate in the study and completed their assessment were included.

They were grouped as follows:

Group 1 (healthy controls): 32 patients.

Group 2 (stage 2-4 CKD): 34 patients.

Group 3 (stage 5 CKD, dialysis): 46 patients, with a mean dialysis duration of 8 months (range: 0.6-48 months); 16 patients were on hemodialysis, and 30, on PD.

Group 4 (kidney transplant recipients): 55 patients, with an average renal graft survival of 3.1 years (range: 0.6-11).

Table 1 shows the detailed characteristics of the different studied groups.

No statistically significant differences were observed in terms of the season of the year when 25(OH)D levels were measured. Among study patients who were taking vitamin D supplements, only those on dialysis showed a statistically significant difference (*Table 1*).

Deficiency of 25(OH)D was detected in 12.5% (4/32) of subjects in group 1 (healthy controls) and 32% (44/135) of CKD patients (p= 0.025).

Among the different subgroups of children with CKD, 23% of patients from group 2 (stage 2-4 CKD), 51% from group 3 (stage 5 CKD), and 22% from group 4 (kidney transplant recipients) had 25(OH)D deficiency. The mean 25(OH)D level of dialysis patients was significantly lower than in the other groups (*Figure 1*).

Patients who had 25(OH)D deficiency showed higher PTH intact molecule values, higher phosphatemia levels, and a lower GFR. Also, 25(OH)D deficiency was more likely in patients who had FSGS as a cause of CKD, hypoalbuminemia, and who came from the North or West (Cuyo) region of Argentina (*Table 2*).

Table 3 sums up the multivariate logistic regression analysis done to establish predictors of 25(OH)D deficiency.

Significant predictors included advanced-stage CKD and place of origin from the Northwest region of Argentina.

The confidence interval range is too large for the albumin lower than 2.5 g/dL covariate; although this result is statistically significant, it suggests the need for a larger sample size to improve estimations.

The PTH intact molecule was significantly higher in the group of patients with CKD and 25(OH)D lower than 20 ng/mL and was inversely correlated with 25(OH)D levels (r: -0.33, p= 0.0005).

DISCUSSION

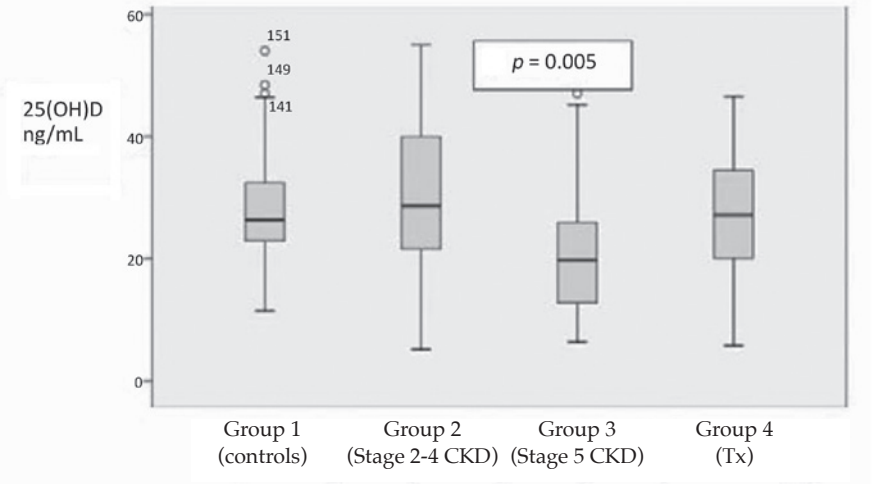
The main finding of this study was the presence of 25(OH)D deficiency in 32% of patients from the CKD groups. Such prevalence is significantly higher when compared to healthy children and adolescents (control group) with similar characteristics in terms of age, sex, and place of origin, who had a 12% 25(OH)D deficiency.

TABLE 1. *Clinical characteristics of studied patients (n: 167)*

Clinical characteristics	Group 1 Healthy controls (n= 32)	Group 2 Stage 2-4 CKD (n= 34)	Group 3 Stage 5 CKD (n= 46)	Group 4 Tx (n= 55)	*P* value
Mean age SD (years old)	10.9 (± 4.5)	10 (± 5)	10.3 (± 5)	11.5 (± 4.5)	0.39
Boys	56%	64%	50%	58%	0.98
Congenital urinary tract abnormalities	-	17 (50%)	20 (43%)	29 (52%)	0.90
FSGS	-	2 (6%)#	12 (26%)#	7 (13%)	0.015*
HUS	-	4 (13%)	4 (9%)	6 (11%)	0.25
Other causes	-	10 (30%)	10 (22%)	13 (24%)	0.26
PTH intact molecule (mean, SD) (pg/mL)	34.8 ± 16#	141 ± 142#	560 ± 400#	80 ± 42	< 0.0001*
25(OH)D (mean, SD) (ng/mL)	28.9 ± 10.7	32 ± 14.7#	22 ± 13#	27.4 ± 11.2	0.005*
Calcemia (mean, SD) (mg/dL)	9.79 ± 0.4#	9.83 ± 0.6#	9.09 ± 0.9#	9.54 ± 0.4	0.00001*
Phosphatemia (mean, SD) (mg/dL)	4.5 ± 0.7#	4.8 ± 0.9	5.9 ± 1.4#	4.7 ± 0.7	0.00009*
Z-score (mean, SD)	0.16 ± 0.1#	-1.32 ± 1.69*	-1.62 ± 1.59#	-1.96 ± 1.69#	< 0.0001*
Vitamin D supplement (400 IU)	0%	9 (26%)	18 (42%)*	9 (17%)*	0.021*
GFR (mL/min/1.73m2) (mean, SD)	100 ± 15#	33.3 ± 18#	-	77.8 ± 27	< 0.0001*
BMI (mean, SD)	18 ± 7.5	17 ± 5	16.8 ± 2.3#	20.4 ± 5.5#	0.001*

IU: international units.
Values with * show statistically significant differences. Values with # show differences among groups.
CKD: chronic kidney disease; Tx: kidney transplant; HUS: hemolytic uremic syndrome; FSGS: focal segmental glomerulosclerosis; SD: standard deviation; GFR: glomerular filtration rate; PTH: parathormone; BMI: body mass index.

FIGURE 1. *Box-and-whisker plot for vitamin D levels corresponding to study patient groups (controls, stage 2-4 chronic kidney disease, stage 5 chronic kidney disease receiving hemodialysis or peritoneal dialysis, kidney transplant recipients)*



P values were estimated using an analysis of variance with multiple post hoc comparisons.
* p = 0.005 for 25(OH)D levels for patients with stage 2-4 versus stage 5 (dialysis) chronic kidney disease.
CKD: chronic kidney disease; Tx: kidney transplant.

As mentioned above, vitamin D deficiency is common among children with CKD; our data is consistent with those of previous publications.[11-16]

In the normal population of children and adolescents, 25(OH)D deficiency is also common; approximately 14%-25% of children will have a 25(OH)D level lower than 20 ng/mL.[21,22]

In Argentina, a study conducted in 2009 by Durán et al. to describe the nutritional status of Argentina, reported vitamin D deficiency only in the Patagonia region with 23% of children younger than 2 and 5 years whose level was below 20 ng/mL.[23]

Data published on children with CKD and 25(OH)D deficiency in Latin America are scarce,[17] so a hypothesis may be that vitamin D levels are more adequate in places closer to the Equator.

In our study, there was a higher percentage of vitamin D deficiency in the North and Cuyo regions of Argentina compared to the southern regions. Given its latitude, there are fewer hours of exposure to sunlight in the Patagonia and, therefore, the population of this region has a high risk for vitamin D deficiency. However, in some provinces of this region, including Tierra del Fuego, the population receives vitamin D

TABLE 2. *Characteristics of children with chronic kidney disease as per vitamin D levels (n: 135)*

Characteristic	Overall	25(OH)D < 20 ng/mL	25(OH)D ≥ 20 ng/mL	*P* value
Age (years old)	10.7 ± 4.8	11.4 ± 4.3	10.4 ± 5	0.23
Male	72 (43%)	22 (51%)	50 (54%)	0.73
BMI	18.6 ± 5.2	19.5 ± 5	18.1 ± 5	0.17
Z-score for height	-1.7 ± 1.6	-1.6 ± 1.3	-1.7 ± 1.8	0.73
PTH intact molecule (pg/mL)	118 (66-324)	201	91	0.019*
Calcemia (mg/dL)	9.5 ± 0.7	9.3 ± 0.9	9.6 ± 0.6	0.09
Phosphatemia (mg/dL)	5 ± 1	5.5 ± 1.4	4.9 ± 1	0.009*
GFR (mL/min/1.73 m2)	40.5 ± 39	30.7 ± 40	45 ± 38	0.04*
Samples taken during the winter	15%	19%	12%	0.3
Vitamin D supplement	36 (27%)	18 (45%)	18 (20%)	0.003*
CKD cause				0.002*
Urinary tract abnormalities	66 (49%)	26%	74%	
FSGS	21 (16%)	67%	33%	
HUS	15 (11%)	13%	87%	
Other	33 (24%)	32%	68%	
Hypoalbuminemia	11 (8%)	90%	10%	0.0001*
Argentine region of origin				0.003*
North	9 (7%)	79%	21%	
Center	10 (7.5%)	0%	100%	
Cuyo	3 (2%)	67%	33%	
Buenos Aires	107 (79%)	33%	67%	
Patagonia	6 (4.5%)	17%	83%	

Data are expressed as mean and standard deviation or percentage and patient number. PTH intact molecule is described as median and 25th-75th percentile.
FSGS: focal segmental glomerulosclerosis; HUS: hemolytic uremic syndrome; BMI: body mass index; CKD: chronic kidney disease; GFR: glomerular filtration rate; PTH: parathormone.
Values with * show groups with statistically significant differences.

TABLE 3. *Logistic regression analysis for predictors of 25(OH)D deficiency*

Covariate	Odds ratio (95% confidence interval)	*P* value
CKD cause		
FSGS	1.7 (0.39-8.27)	0.45
North region	5.1 (1.4-18.7)	0.013*
Stage 4 or 5 CKD	2.7 (1.0-7.2)	0.049*
Albumin < 2.5 g/dL	25 (1.8-317)	0.015**

CKD: chronic kidney disease; FSGS: focal segmental glomerulosclerosis.
Values with * show groups with statistically significant differences.
** The confidence interval range is too large; although this result is statistically significant, it suggests the need for a larger sample size to improve estimations.

supplementation during the autumn and winter months.[24]

Regarding the cause of CKD, patients with FSGS has significantly lower 25(OH)D levels; however, in the multivariate analysis, the cause of CKD was not considered a statistically significant outcome measure. The presence of hypoalbuminemia is typical in patients with CKD secondary to FSGS with persistent nephrotic syndrome, and is also common among children undergoing dialysis because of malnutrition or albumin loss from PD fluid. Children with CKD and an albumin level lower than 2.5 g/dL had a higher risk for 25(OH)D deficiency, both in the univariate and the multivariate analyses.

Prior studies have demonstrated that, in these patients, 25(OH)D levels are positively associated with albuminemia and negatively associated with proteinuria.[15,16] Also, 99% of 25(OH)D is bound to albumin and vitamin D-binding protein. In these cases, serum levels of 25(OH)D may not reflect free or bioavailable vitamin D but, in general, these patients are considered to have severe deficiency; this is described, for example, as an increase in PTH intact molecule.

In children with CKD, 25(OH)D deficiency has been correlated to the presence of hyperparathyroidism and short stature, and it may be a modifiable risk factor for patients with high blood pressure following a renal transplant.[12] The studied CKD patients showed significantly higher PTH intact molecule levels and an inverse correlation with 25(OH)D levels. No differences were observed in the height Z-score of patients with and without vitamin D deficiency.

Our study poses some limitations: the small number of healthy controls, and the lack of information regarding hours of exposure to sunlight and vitamin D dietary intake. Children with CKD, especially those undergoing dialysis, are more likely to spend less time outdoors. Anyway, the association between vitamin D deficiency and the season of the year was similar among healthy controls and the different CKD patient subgroups. Vitamin D deficiency is a risk factor for modifiable secondary hyperparathyroidism; therefore, strategies for early detection and prevention during follow-up of children with CKD are required.

CONCLUSION

In this study, the prevalence of 25(OH)D deficiency was 32% in children with CKD; it reached 51% among those with stage 5 CKD (dialysis). Predictors of 25(OH)D deficiency included hypoalbuminemia, advanced CKD, and place of origin from the Northwest region of Argentina. ■

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