original article

Vitamin D insufficiency and deficiency in children with chronic kidney disease

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BACKGROUND AND OBJECTIVES: Hypovitaminosis D is a frequent condition in normal populations. Children with chronic kidney disease (CKD) present a high risk of developing complications due to hypovitaminosis D. Our aim was to determine the frequency of vitamin D insufficiency/deficiency in children with different stages of CKD who were followed up at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia.

DESIGN AND SETTING: University hospital-based case-control study of children followed up between March 2010 and March 2011.

PATIENTS AND METHODS: Blood was extracted from children with CKD to measure urea, creatinine, hemoglobin, calcium, phosphorus, alkaline phosphatase, intact parathyroid hormone (iPTH), and vitamin D3 levels. We calculated correlations between iPTH and vitamin D levels, and associations between vitamin D levels and CKD stages.

RESULTS: The frequency of vitamin D insufficiency/deficiency was high among the cases and controls. Children with CKD had significantly lower levels of vitamin D than their peers with normal kidney function (P=.05) with a mean (SD) level of 17.5 (9.9) ng/mL versus 21.0 (13.4) ng/mL for the control group. Among the children with CKD, 36 (45.0%) had vitamin D insufficiency, 24 (30.0%) had vitamin D deficiency, and 10 (12.5%) had severe deficiency. There was a positive correlation between vitamin D3 level and CKD stages (Kendall tau=0.22, P=.003). A significant association existed between glomerular filtration rate and vitamin D3 deficiency (P=.002). There was a significant negative correlation between iPTH and vitamin D3 concentrations (Spearman correlation coefficient= -0.27, P=.01). A significant association existed between age and vitamin D3 level (P<.0001).

CONCLUSION: Vitamin D insufficiency/deficiency is more frequent in children with CKD than in those with normal kidney function.

Vitamin D insufficiency and deficiency are extremely common conditions observed in normal populations, with an estimated 1 billion people affected worldwide.[1] Hypovitaminosis D is the most common cause of rickets and osteomalacia in adults and children living in the Saudi Arabia.[2,3] There is, however, a paucity of reports evaluating the frequency of this condition in children with chronic kidney disease (CKD) living in Saudi Arabia and in other Arab countries. The aim of this study was to determine the frequency of vitamin D3 insufficiency and deficiency in children with CKD who were followed up at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia.

PATIENTS AND METHODS

We conducted a case-control study to evaluate the vitamin D status in children with CKD who were followed up in the Pediatric Nephrology Clinic at KAUH, between March 2010 and March 2011. The Pediatric Nephrology Service at KAUH is considered a tertiary centre for pediatric nephrology in the western province of Saudia Arabia. A control population of children with normal kidney function, who visited the hospital for other reasons, was also identified. Consent was obtained from the parents of the participants prior to their inclusion in the study. The study was approved by the Biomedical Ethics Research Committee of KAUH.

For the case group, we included all children with

CKD, irrespective of the stage of the disease. Exclusion criteria were evidence of one chronic liver disease, defined as the presence of peripheral stigmata such as clubbing, jaundice, palmar erythema, hapatomegaly/shrunken liver and splenomegaly or elevated liver enzymes for more than 6 months without clinical signs;[4] (2) gastrointestinal malabsorption, defined as the presence of nutrients in the feces, followed by loss or insufficient gain of weight, with a diet that was appropriate for the age;[5] (3) nephrotic syndrome or marked proteinuria; (4) a history of anticonvulsant therapy; or (4) consumption of large doses of cholecalciferol in the preceding 2 years. None of the patients was receiving ergocalciferol or cholecalciferol supplementation at the time of recruitment. For the control group, we randomly selected children who visited the hospital for other reasons. We included children who had normal kidney function, evaluated by measuring blood urea nitrogen and serum creatinine.

Patients were classified according to the severity of their CKD and estimated glomerular filtration rate (EGFR) into five stages, from stage 1 to stage 5 CKD.

We did blood tests in all children to measure urea, creatinine, hemoglobin (HEP), calcium, phosphorus, alkaline phosphatase (ALP), intact parathyroid hormone (iPTH), and calcidiol (vitamin D3). Calcidiol levels were measured by radioimmunoassay (Diasorin, Stilwater, Minnesota, United States).

Based on the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, vitamin D sufficiency was defined as a 25-hydroxyvitamin D [25(OH)D] level ≥30 ng/mL; insufficiency, 16-29 ng/mL; deficiency, 5-15 ng/mL; and severe deficiency if <5 ng/mL.[6] Serum iPTH was measured by Elecsys 2010 autoanalyzer system (Roche Diagnostics, Basel, Switzerland). The eGFR was calculated using the Schwartz Formula.[7] We categorised the subjects according to their eGFR values, and CKD stage was determined based on the National Kidney Foundation guidelines as: stage 1 (≥90 mL/min/1.73 m^2), stage 2 (60 to 89 mL/min/1.73 m^2), stage 3 (30 to 59 mL/min/1.73 m^2), stage 4 (15 to 29 mL/min/1.73 m^2), and stage 5 (<15 mL/min/1.73 m^2).[6]

Baseline continuous variables were expressed as medians (interquartile range). Categorical variables were expressed as frequencies (percentages). Comparisons between groups were performed using nonparametric ANOVA for continuous variables andtthe Fisher exact test for categorical variables. The Spearman correlation coefficient was used to calculate the correlations between iPTH and vitamin D levels.The Kendall tau was used to measure the association between vitamin D levels and CKD stages. The t test was used to compare the results between cases and controls. The significance level was set at $P<.05$. Owing to the exploratory nature of the present study, no adjustment for multiplicity was made. All tests were performed using SAS 9.2 software (SAS Institute, Cary, North Carolina, United States).

RESULTS

One hundred and sixty-five children were enrolled in the study; 80 cases (52 boys and 28 girls) and 85 controls (41 boys and 44 girls). In the case group the ages varied from 1-15 years, with a mean (SD) age of 8.6 (4.7) years. The children in the control group were aged 1-16 years, with mean (SD) age of 6.4 (3.6) years. The children in both groups were of different nationalities. For the case group 50 (62.5%) were of Saudi nationality, 23 (28.8%) were non-Saudis (13 Yemeni, 2 Syrian, 3 Sudanese, 2 Egyptian, 2 Palestinian and 1 Moroccan), and 7 (8.7%) were Asian (3 Afghani, 2 Pakistani and 2 Indian). For the control group, 30 (35.3%) were of Saudi

Table 1. Levels of 25(OH) D3 at different stages of chronic kidney disease.[a]

Stage of chronic kidney disease	Vitamin D3 (ng/mL)	Normal (n=10) 36.0 (5.8)	Insufficient (n=36) 20.7 (4.0)	Deficient (n=24) 10.8 (3.1)	Severely deficient (n=10) 3.8 (0.8)	*P*
Stage 1 (n=17)	16.8 (9.0)	2 (20)	7 (19.4)	8 (33.3)	0 (0)	.003
Stage 2 (n=12)	23.2 (10.2)	3 (30)	6 (16.7)	3 (2.5)	0 (0)	
Stage 3 (n=11)	14.6 (8.8)	1 (10)	5 (13.9)	4 (16.7)	1 (10)	
Stage 4 (n=16)	22.9 (9.3)	3 (30)	9 (25.0)	4 (16.7)	0 (0)	
Stage 5 (n=5)	20.0 (10.4)	1 (10)	3 (8.3)	0 (0.0)	1 (10)	
Hemodialysis (n=10)	15.6 (6.9)	0 (0)	5 (13.9)	4 (16.7)	1 (10)	
Peritoneal dialysis (n=9)	6.2 (5.8)	0 (0)	1 (2.8)	1 (4.2)	7 (70)	

[a]Data are presented as mean (SD) and frequency (percentage).

nationality, 30 (35.3%) were non-Saudis (22 Yemeni, 2 Syrian, 2 Sudanese, 1 Egyptian and 3 Palestinian), 20 (22.5%) were Asian (6 Bengali, 2 Afghani, 7 Pakistani, 3 Indian and 1 Filipino), and 4 were Africans (2 Chadian, 1 Somali and 1 Malian).

Seventeen patients (21.3%) had stage 1 CKD, 12 (15.0%) had stage 2 CKD, 11 (13.8%) had stage 3 CKD, 16 (20.0%) had stage 4 CKD and 24 (30.0%) had stage 5 CKD. Among the 24 patients who had stage 5 CKD, 5 were managed conservatively, 10 were on hemodialysis (HD), and 9 were on peritoneal dialysis (PD) (**Table 1**). The underlying cause of CKD was obstructive uropathy in 52 children (65%), glomerular disease in 6 children, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) in 2 children (1 child had stage 4 CKD; the other had stage 5 CKD and was on HD), oxalosis in 1 child, Fanconi syndrome in 1 child, familial hemolytic uremic syndrome in 1 child (the patient had stage 5 CKD and was on PD), renal cystic dysplasia in 3 children, chronic pyelonephritis in 4 children, and unknown in 10 children.

In the case group, only 10 (12.5%) patients had normal vitamin D3 level >30 ng/mL, with a mean (SD) of 17.5 (9.9) ng/mL. Thirty-six (45.0%) patients had vitamin D insufficiency with a mean (SD) of 20.6 (3.9) ng/mL, 24 (30.0%) had vitamin D deficiency with a mean (SD) of 10.8 (3.1) g/mL, and 10 (12.5%) had severe deficiency with a mean (SD) of 3.8 (0.8) ng/mL (**Table 1**). In the control group, 16 (18.8%) children had normal vitamin D3 levels; 36 (42.4%) were insufficient,

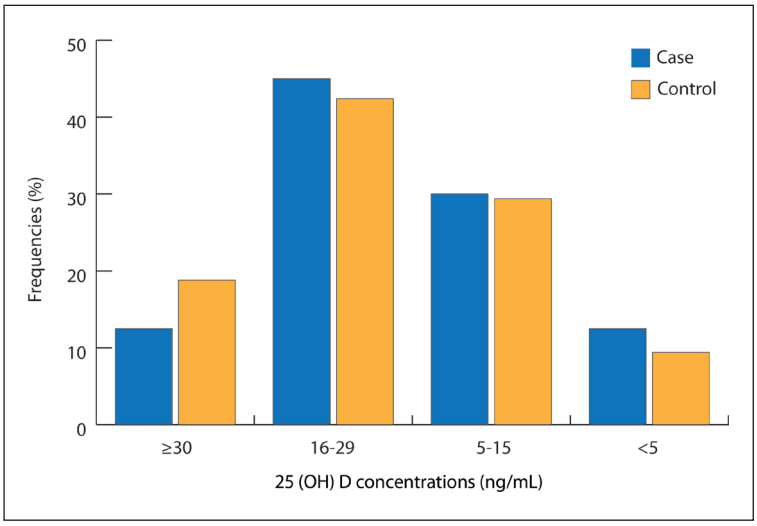

Figure 1. Percentage of children in case and control groups according to vitamin D3 status.

Table 2. Levels of serum calcium, phosphorus, ALP and haemoglobin according to vitamin D3 status in the case group.[a]

Variables[b]	Vitamin D levels (ng/mL)				*P*
	Normal (n=10)	Insufficient (n=36)	Deficient (n=24)	Severely deficient (n=10)	
Age	2.3 (1; 8)	6 (3; 10.5)	12.5 (9.5; 15)	10 (9; 14)	<.0001
Body mass index	15.4 (12.3; 18.1)	15.5 (14.1; 17.0)	16.6 (14.3; 20.2)	14.3 (13.8; 15.3)	.10
Hemoglobin	11.4 (10; 12)	11.2 (9.4; 12.2)	12.3 (11.5; 13.2)	10.2 (9; 11)	.005
Glomerular filtration rate	60 (26; 69)	31.5 (14; 76.5)	51 (21; 101.5)	5 (5; 5)	.002
Serum creatinine	83 (55; 136)	153.5 (53.5; 282.5)	126.5 (49.5; 319.5)	776 (407; 856)	.004
Intact parathyroid hormone	8.6 (2.4; 12.6)	9.5 (3.7; 24.7)	10.2 (4.9; 28.7)	69.2 (23.1; 166.9)	.012
Calcium	2.4 (2.1; 2.7)	2.4 (2.2; 2.4)	2.27 (2.18; 2.33)	2.23 (1.8; 2.4)	.08
Phosphate	1.5 (1.4; 1.9)	1.6 (1.4; 1.9)	1.5 (1.3; 1.7)	1.9 (1.5; 2)	.17
Alkaline phosphatase	246 (156; 309)	221.5 (199; 286.5)	269 (207; 347.5)	326 (157; 612)	.28
Sex (Boys)	8 (80.0)	26 (72.2)	14 (58.3)	4 (40.0)	.19

[a]Data are presented as median (interquartile range) and frequency (percentage).

[b]References ranges for laboratory values: ALP (50-136 U/l), Ca (2.1-2.5 mmol/L), GFR (90-120 mL/minute/1.73 m2), Hb (11-13 g/dL), PO4 (0.81-1.58 mmol/L), iPTH (1.6-6.9 pmol/L) and sCreat (8-31 µmol/L).

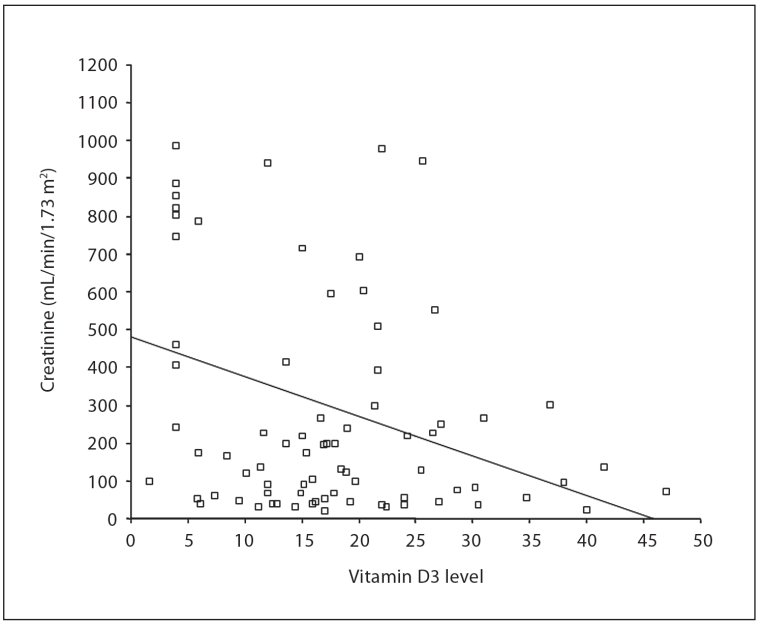

Figure 2. Relationship between serum creatinine and vitamin D3 level in children with chronic kidney disease.

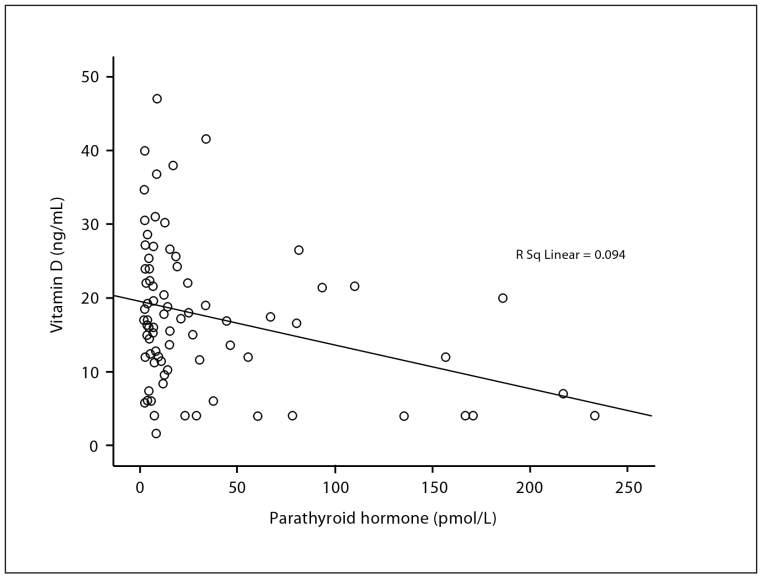

Figure 3. Correlation between vitamin D3 and parathyroid hormone levels in children with chronic kidney disease.

25 (29.4%) were deficient, and 8 (9.4%) were severely deficient (**Figure 1**). The mean (SD) vitamin D3 level in this group was 21.0 (13.4) ng/mL. Low vitamin D3 levels were common in both groups, but these were more frequent among children with CKD; 87.5% against 81.2% for the control group. In addition, vitamin D3 levels were significantly lower in children with CKD than in those with normal kidney function; mean (SD) level of 17.5 (9.90) ng/mL against 21.0 (13.43) ng/mL for the control group (P=.05).

We found a lower vitamin D3 level in PD children compared with children receiving conservative treatment. The mean (SD) vitamin D3 level in PD patients was 6.2 (5.8) ng/mL (**Table 1**), and there was a negative correlation between vitamin D3 levels and the stage of CKD (P=.003). A negative correlation also existed between vitamin D3 and serum creatinine levels (P=.004) (**Table 2, Figure 2**). There was a significant association between vitamin D3 level and GFR (P=.002) (**Table 2**). We also found that all PD and HD patients had either vitamin D3 insufficiency or deficiency.

There was a significant association between age and vitamin D3 deficiency (P<.0001) (**Table 2**). Table 2 also summaries the level of serum calcium, phosphorus, ALP and hemoglobin in the different groups of children with CKD according to their vitamin D3 status. There was no significant difference between the groups in serum calcium, phosphorous, or ALP. However, we found a significant negative correlation between iPTH level and vitamin D3 concentrations (P=.012) (**Figure 3**) and a negative correlation between iPTH and the GFR (P=.01). No such observation was made in the controls. The iPTH levels of the controls were within normal ranges, with a mean (SD) iPTH level of 4.2 (2.3) pmol/L (reference range, 1.6-6.9 pmol/L).

DISCUSSION

This hospital-based study confirmed that vitamin D deficiency and insufficiency are more common in children with CKD than in healthy children. The high frequency of vitamin D3 insufficiency and deficiency observed in both groups of children in this study can be attributed to lack of sun exposure, poor supplementation, consumption of cola soft drinks and prolonged breastfeeding,[3,8,9] which are common practices in Saudi Arabia. The finding that vitamin D deficiency was more common among cases than controls can be due to the fact that in addition to the above reasons, disturbances in vitamin D metabolism occur in children with CKD.[10,11] A high proportion of children with CKD were also reported to be vitamin D3 deficient/insufficient in hospital-based studies conducted in different parts of the world; 87.0% in children of South Asian origin in Manchester,[10] 77.2% in children with stages 2-4 CKD in Michigan,[11] 60.0% in pediatric patients with all stages of CKD in Miami,[12] and 82.1% in children with stages 2-4 CKD in New Delhi.[13]

In general, the recommended dietary allowance for vitamin D intake that is sufficient to maintain bone health and normal calcium metabolism in healthy people increases with age. In Saudi Arabia, older children tend to consume dairy products less than their younger peers. This could explain why we observed a lower vitamin D3 levels in older children. However, other factors may be involved as there are no considerable differences in the recommended dietary allowance of vitamin D in children within the same age group. The Food and Nutrition Board, for example, categorize children into two groups based on the recommended dietary allowances of vitamin D; 400 IU for children between 0-12 months and 600 IU for those aged 1-13 years.[14] The children in our study were within the same age group according to this classification.

It is known that patients with CKD are prone to develop hypovitaminosis D because of declining renal function. In addition, dietary restriction of phosphorus is recommended in children with CKD stages 3 to 5, who have serum PTH levels above the target range for the stage of CKD and those on dialysis.[15] While low levels of phosphorus are advised in dialysis patients, this could have a negative effect on the vitamin D status of the patients as there is evidence that phosphorus levels also play an important role in the renal production of 1,25(OH)2D.[16] In this study, all the children on dialysis had suboptimal vitamin D3 levels, and most cases (70%) of severe vitamin D deficiency were observed in children on PD. Although there are few data evaluating the magnitude of vitamin D deficiency in children on dialysis, the findings in this study are in line with those reported from studies conducted in adult patients. Shah et al conducted a study in adult patients on PD and reported that all the patients were either deficient or insufficient; 86% had undetectable vitamin D levels.[17] In another study, the authors found that 97% of their patients on HD had vitamin D3 levels in the suboptimal ranges.[18] The severity of vitamin D deficiency was higher in patients undergoing maintenance HD as compared with patients with stages 1 to 5 CKD, who did not require dialysis.

We observed a significant negative correlation between iPTH levels and 25(OH)D3 concentrations (P=.012). High PTH levels are common in patients with CKD.[11,19] As kidney function deteriorates, the serum levels of 1,25(OH)2D decrease and finally secondary hyperparathyroidism develops. During this process, disturbances of calcium and phosphorus metabolism occur (hypocalcemia and hyperphosphatemia), which contribute to the aggravation of hyperparathyroidism and renal bone disease.[15] The K/DOQI guidelines recommend the measurement of serum PTH, calcium, and phosphorus when GFR falls below stage 2 CKD levels and to subsequently monitor these parameters in patients with CKD.[15]

In our study there was no significant difference in serum calcium, phosphorus, hemoglobin or GFR levels between patients with normal versus insufficient vitamin D3 levels. However, decreases in vitamin D3 levels were associated with declining GFR. This contradicts the findings of a previous study that demonstrated that vitamin D3 deficiency occurred at all stages of CKD, but it was not necessarily altered by decreases in GFR. The authors also found that low levels of GFR (below 50 mL/min/1.73 m^2) are not associated with changes in the serum calcium and phosphorus.[20] On the contrary, 1,25(OH)D decreases early in the disease and progressively declines thereafter.

Vitamin D insufficiency and deficiency are issues of concern in patients with CKD. The metabolic disturbances due to vitamin D insufficiency/deficiency result in increased bone remodeling, subsequent hyperparathyroidism and increased alkaline phosphatase levels.[21] In an attempt to normalise PTH levels and hence prevent renal bone disease, clinicians might be tempted to prescribe high doses of vitamin D analogs in patients with hypovitaminosis D. In fact, some authors suggest that early treatment with ergocalciferol[11] or high-dose (600 000 IU) cholecalciferol supplementation[13] has proven effective in normalizing PTH levels and hence preventing renal bone disease. However, caution must be taken when administering vitamin D treatment as the use of high doses of the drug can be potentially harmful. There is evidence that treatment with cholecalciferol, the most frequently prescribed vitamin D analog, causes significant absorption of calcium and phosphorus, with the consequent risk of hypercalcemia. This might cause an increase in vascular calcification and an increase in cardiovascular mortality risk in some cases.[22]

This study has some limitations because it is a single center study. However, the findings in this study can be extrapolated to children with CKD in other regions of Saudi Arabia or other Arab countries because our unit is considered a referral center for the Western Province of the country. In conclusion, vitamin D insufficiency and deficiency are more common in children with CKD than in those with normal kidney function. We support the K/DOQI pediatric guidelines to measure 25(OH)D3 levels in children with CKD to decrease complications resulting from vitamin D3 deficiencies.

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