Vitamin D insufficiency and treatment with oral vitamin D3 in children with chronic kidney disease

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ABSTRACT

الأهداف: دراسة الآثار المترتبة من العلاج بفيتاين د (كوليكالسيفيرول) عن طريق الفم على مستويات فيتامين د3 ومستوي هرمون الغدة الجار درقية (iPTH) في الأطفال الذين يعانون من مرض الكلى المزمن.

الطريقة: أجرينا هذه الدراسة الوصفية الاستطلاعية الغير منضبطة في عيادة الكلى للأطفال، مستشفى جامعة الملك عبدالعزيز، جدة، المملكة العربية السعودية وذلك خلال الفترة من يناير إلى أكتوبر 2011م. لقد تم قياس نسبة 25 هيدروكسي فيتامين د3 و هرمون الغدة الجار درقية في مصل الأطفال الذين يعانون من الفشل الكلوي المزمن من المرحلة الثانية وحتى الخامسة. ثم بدأ إعطاء هؤلاء الأطفال فيتامين د3 (كوليكالسيفيرول) 2000 وحدة دولية عن طريق الفم يومياً. و بعد 3 ثم 6 أشهر تم إعادة تقييم نسبة 25 هيدروكسي فيتامين د3 وهرمون الغدة الجار درقية مرة أخرى مع تحليل لنسبة وظائف العظام (الكالسيوم والفوسفات وإنزيم الفوسفات القلوي) و كذلك نسبة الكرياتينين.

النتائج: شملت هذة الدراسة على 45 طفلاً متوسط أعمارهم 9.6 (4.6) عاماً (31 طفل و 14 طفلة). لقد كان هناك تحسن كبيرفى مستوى فيتامين د3 بعد 3 أشهر من العلاج وذلك من المتوسط 14.2 (8.2) إلى 20 (11.1) نانوغرام/ملليتر (p<0.001). ولكن لم يصل الى المستوى الطبيعي (30 نانوغرام/ملليتر) إلا في 5 أطفال. ولم يلاحظ المزيد من التحسن بعد 6 أشهر من العلاج حيث كان متوسط مستوى فيتامين د3 20.17 (13.4) نانوغرام/ملليتر (p=0.65). ولم يكن هناك تحسن في معدلات هرمون الغدة الجار درقية المرتفعة بعد مرور 3 و6 أشهر من العلاج. كما لم يلاحظ أي تغييرات في وظائف العظام ومستوى الكرياتينين.

خاتمة: أظهرت هذه الدراسة بأن إعطاء فيتامين د3 2000 وحدة دولية يومياً عن طريق الفم في الأطفال المرضى بالفشل الكلوى أدى الى تحسين مستواه بالدم لكنة لم يصل بعد إلى المعدل الطبيعي إلا في عدد قليل منهم (11%)، مع عدم تحسن في معدل هرمون الغدة الجار درقية المرتفع لديهم.

Objectives: To investigate the effects of oral cholecalciferol on the levels of vitamin D3 and intact parathyroid hormone (iPTH) in children with chronic kidney disease (CKD).

Methods: We conducted a prospective uncontrolled observational study at the Pediatric Nephrology Clinic of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia between January and October 2011 to assess serum 25-hydroxyvitamin D3 (25[OH]D) and iPTH in children with CKD stages 2-5. Children with low vitamin D3 levels were commenced on cholecalciferol, 2000 IU/day. Their 25(OH)D3 and iPTH levels were reassessed, first after 3 months, then after 6 months. Data analysis was performed using the Statistical Package for Social Sciences. Paired t-test was used to compare results before and after treatment.

Results: Forty-five children (31 boys and 14 girls) were included in the study. Their mean±SD age was 9.6 ± 4.6 years. There was significant improvement in 25(OH)D3 after 3 months (14.2 ± 8.2 - 20 ± 11.1 ng/mL) (p<0.001). However, only 5 children reached levels ≥30 ng/mL. There was no further improvement after 6 months of treatment (20.17 ± 13.4 ng/mL) (p=0.65). There was no improvement in iPTH levels after 3 and 6 months. No changes were also observed in the levels of calcium, phosphate, alkaline phosphatase, or creatinine.

Conclusion: The administration of oral vitamin D3 at 2000 IU/day resulted in significant improvement of vitamin D levels in children with CKD, but normalized only in 11% of the patients. The treatment had no effect on iPTH levels.

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Children with chronic kidney disease (CKD) are at risk of renal bone disease (RBD), which starts early in the disease.[1] Defective skeletal mineralization is associated with lower serum calcium levels and increased intact parathyroid hormone (iPTH) concentrations that result from phosphate retention and impaired conversion of 25-hydroxyvitamin D3 (25[OH]D3) to 1,25-dihydroxyvitamin D3 (1,25[OH]2D3).[2] An elevated level of fibroblast growth factor 23 (FGF-23) was reported as an early indicator of defects in skeletal mineralization in the course of CKD.[3] The FGF-23 is a bone-derived hormone that plays an important role in inducing urinary phosphate excretion and suppressing 1,25(OH)2D3 synthesis in the presence of fibroblast growth factor receptor 1 (FGFR1), and its co-receptor Klotho.[4] In CKD, circulating FGF-23 levels are progressively increased to compensate for persistent phosphate retention, but this results in reduced renal production of 1,25-dihydroxyvitamin D and leads to hypersecretion of PTH.[3,4] Recently, 25(OH)D3 deficiencies were reported in both adults,[5,6] and children[7,8] with CKD. We previously reported a high frequency (87.5%) of vitamin D insufficiency/deficiency in children with CKD that was negatively correlated with iPTH levels and the stages of CKD.[9] The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the management of CKD-mineral and bone disorder (CKD-MBD) recommended that the level of 25(OH)D3 should be monitored, and if it is low, ergo- or cholecalciferol supplements should be prescribed.[10] Shroff et al[11] demonstrated in a randomized, double-blinded, placebo-controlled study that ergocalciferol is safe and effective in delaying the onset of secondary hyperparathyroidism in 25(OH)D3 deficient children with CKD stages 2-3, who are not receiving alpha-calcidol. In this study, we aim to investigate the effect of daily oral vitamin D3 on the levels of 25(OH)D3 and iPTH in vitamin D insufficient/deficient children with CKD who were receiving alpha-calcidol. We are testing the hypothesis that in children with CKD on alpha-calcidol, who are vitamin D insufficient/deficient, treatment with oral cholecalciferol could be helpful in normalizing vitamin D3 levels and in preventing CKD-MBD.

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Methods. In a prospective uncontrolled observational study, we included children with CKD stages 2-5 who were followed up at the Pediatric Nephrology Clinic of King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia (KSA) between January and October 2011. The KSA is a very sunny country throughout the year. Ethical approval for the study was obtained from the Biomedical Ethics Research Committee of King Abdulaziz University.

Out of 55 children with CKD stages 2-5 who suffered from vitamin D3 insufficiency/deficiency, only 45 children with CKD stages 2-5 whose parents gave their consent were included in the study. All the children were available for vitamin D3 level assessment and bone profile tests after 3 months of treatment, but only 32 were available for assessment after 6 months. Blood tests were carried out in all children to measure urea, creatinine, calcium (Ca), phosphate (PO_4), alkaline phosphatase (ALP), iPTH, and calcidiol (vitamin D3). Calcidiol levels were measured using radioimmunoassay (Diasorin Inc, Stillwater, MN, USA). Serum iPTH was measured by Elecsys 2010 autoanalyzer system (Roche Diagnostics, Basel, Switzerland). The stages of CKD were classified according to the estimated glomerular filtration rate (eGFR). The eGFR was calculated using the Schwartz Formula.[12] All the children had received alpha-calcidol (15-30 nanograms/kg/day) and calcium carbonate (300 mg-1.25 gm, 3-4 times a day) as phosphate binder for at least 3 months prior to their inclusion in the study. Oral vitamin D3 (cholecalciferol) was prescribed to all children at a dose of 2000 IU/day (20 drops a day). Blood tests were repeated after 3 months of treatment, then after 6 months under the same treatment to measure the levels of vitamin D3, iPTH, Ca, PO_4 and ALP. Based on the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, vitamin D sufficiency was defined as: 25(OH)D level ≥30 ng/mL; insufficiency - 16-29 ng/mL; deficiency - 5-15 ng/mL; and severe deficiency - <5 ng/mL.[13]

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA) version 18. Paired t-test was used to compare the results of 25(OH)D3 levels before and after treatment. Results were expressed as mean ± SD, and $p<0.05$ was considered significant.

Results. Forty-five children were included in this study (31 boys and 14 girls). Their age was 9.6 ± 4.6 years (median - 10 years; range - one to16 years). Thirty-three children were Saudis, and the others were of various nationalities. Based on the stage of kidney disease, 12 children had stage 2 CKD, 6 had stage 3

CKD, 9 had stage 4 CKD, and 18 had stage 5 CKD (10 were on hemodialysis [HD], and 8 on peritoneal dialysis [PD]). The underlying etiology of CKD was obstructive uropathy and congenital abnormalities of the renal tract in 25 children, glomerular disease in 3 children, hereditary renal tubular disease in 4 children, inherited cystic kidney diseases in 4 children, atypical hemolytic uremic syndrome in one child, and the underlying cause was unknown in 8 children. According to the baseline 25(OH)D3 levels, 18 children were vitamin D3 insufficient, 18 were deficient, and 9 had severe vitamin D3 deficiency. All children were available for vitamin D3 level assessment and bone profile tests after 3 months of treatment, but only 32 were available for assessment after 6 months. The levels of 25(OH)D3 in the children increased significantly after 3 months of treatment (14.2 ± 8.2 - 20 ± 11.1 ng/mL) (p<0.001), however, only 5 children (11% [n=45]) had vitamin D3 levels ≥30 ng/mL. There was no further improvement in the levels of vitamin D3 in 32 children who were available for blood tests after 6 months of treatment. The levels of iPTH did not improve after 3 and 6 months of treatment. No changes were also observed in the levels of Ca, PO_4, ALP, or creatinine. **Table 1** gives a summary of the changes in the blood levels of 25(OH)D3, iPTH, Ca, PO_4, ALP and creatinine after 3 and 6 months of treatment with oral cholecalciferol in 32 children who completed the study. When we classified the children according to their initial vitamin D levels and evaluated their response, we found that the best response was in children with vitamin D3 insufficiency (n=18; 40%). There was a significant improvement in their 25(OH)D3 levels (p=0.032) with 5 children (27.8%) attaining normal levels after 3 months of therapy. Among the patients with 25(OH)D3 insufficiency, 5 had stage 2 CKD, one child had stage 3 CKD, 7 had stage 4 CKD, and 5 had stage 5 CKD and were on PD. After 3 months of treatment, normal vitamin D3 levels were achieved in 2 children with stage 2 CKD, in 2 children with stage 4 CKD, and in one child with stage 5 CKD. **Table 2** shows a comparison of the 25(OH)D3 levels in patients after 3 and 6 months of treatment based on the stage of CKD. In the vitamin D3 deficient group, 7 children had stage 2 CKD, 5 had stage 3 CKD, 2 had stage 4 CKD, and 5 had stage 5 CKD and were on dialysis. All 9 children who had severe vitamin D3 deficiency had stage 5 CKD and were on dialysis. There was a significant improvement in the levels of vitamin D3 in both groups (deficient and severely deficient), but none of the children attained normal vitamin D3 levels (p=0.001 in the deficient and p=0.002 severely deficient groups) (**Table 3**).

Discussion. Data from this study shows that the daily administration of low doses of oral vitamin D3 for 3-6 months resulted in significant improvement

Table 1 - Results of laboratory investigations initially and after 3 and 6 months of treatment in 32 children with chronic kidney disease.

Parameter	Start=0	3 months	(95% CI of difference)		*P*-value	6 months	(95% CI of difference)		*P*-value
	mean ± SD	mean ± SD	Lower	Upper		mean ± SD	Lower	Upper	
Vitamin D3 (25[OH]D3), ng/ml	14.20 ± 8.2	18.13 ± 12.5	3.391	8.213	<0.001	20.17 ± 13.4	3.377	5.274	0.65
iPTH, pmol/L	56.40 ± 10.4	79.70 ± 16.4	3.617	33.85	0.110	74.9 ± 14.2	21.11246	30.92113	0.703
Calcium, mmol/L	2.30 ± 0.3	2.30 ± 0.3	0.33	1.07	0.3	2.60 ± 0.3	0.095	0.046	0.5
Phosphate, mmol/L	1.70 ± 0.6	1.70 ± 0.6	4.98	15.21	0.31	1.66 ± 0.5	0.1358	0.193	0.72
ALP, U/L	331.50 ± 37.3	322.10 ± 40.5	29.04	56.04	0.530	318.00 ± 38	35.9781	44.2541	0.84
Creatinine, micromol/L	345.30 ± 44.3	324.40 ± 44.3	2.96	104.53	0.120	283.90 ± 37	25.63	106.53	0.225

Data are presented as mean ± SD unless otherwise stated. The levels of 25 hydroxyvitamin D3 - 25(OH)D3; iPTH - intact parathyroid hormone; PO_4 - phosphate; ALP - alkaline phosphatase; and creatinine were measured prior to the administration of oral cholecalciferol (2000 IU/day) and after 3 months of treatment. Reference ranges for laboratory values: ALP (145-450 U/L); Ca (2.1-2.5 mmol/L); PO_4 (0.81-1.58 mmol/L); iPTH (1.6-6.9 pmol/L); and creatine (8-31 micromol/L)

Table 2 - Comparison of the 25 hydroxyvitamin D3 levels after 3 treatments based on the stage of chronic kidney disease (CKD).

CKD stage	Start=0, ng/ml	3 months, ng/ml	95% CI of difference		*P*-value
			Lower	Upper	
Stage 2, n=12	16.80 ± 7.9	22.34 ± 9.5	1.57	9.512	0.011
Stage 3, n=6	11.72 ± 4.7	18.78 ± 5.7	0.014126	14.12	0.050
Stage 4, n=9	19.61 ± 7.5	30.86 ± 26.8	7.26	29.77	0.202
Stage 5, n=18	10.44 ± 7.6	17.25 ± 13.0	1.76	11.850	0.011

Data are presented as mean ± SD unless otherwise stated. The mean ± SD of 25-hydroxyvitamin D3 levels are in ng/ml.

Table 3 - Classification according to the baseline 25-hydroxyvitamin D3 and intact parathyroid hormone levels.

Baseline	25 hydroxyvitamin D3					Intact parathyroid hormone				
	Start=0, ng/ml	3 months, ng/ml	95% CI of difference		*P*-value	Start=0,	3 months, pmol/L	95% CI of difference		*P*-value
			Lower	Upper				Lower	Upper	
Insufficiency (16-29 ng/mL), n=18	20.1 ± 3.7	29.85 ± 21.7	1.695	12.647	0.032	93.4 ± 87.7	88.7 ± 93	45.088	46.196	0.20
Deficiency (5-15 ng/mL), n=18	10.6 ± 3.4	15.9 ± 5.7	2.33312	7.86466	0.001	47.2 ± 68.5	61.3 ± 67.8	23.24548	50.69048	0.22
Severe deficiency (<5 ng/mL), n=9	4 ± 7.4	13.5 ± 6	4.52876	14.47274	0.002	122.3 ± 98.2	118.2 ± 83.7	44.482	55.843	0.43

Data are presented as mean ± SD unless otherwise stated

(p<0.001), but not in normalization of vitamin D3 levels in most children with CKD. Our findings is different from that of Shroff et al[11] who used higher doses of oral vitamin D3 in vitamin D deficient or severely deficient children with CKD, who had normal iPTH levels. They used intensive replacement treatment of ergocalciferol as per KDOQI clinical practice guidelines for nutrition in CKD[14] for 3 and 6 months found that after 3 months of therapy, there was a significant improvement in 25 (OH)D levels in the treated group as compared with the placebo group (median of 56 versus 96.5 nmol/L, p=0.0001). There was also an improvement in the levels of 1,25(OH)2D levels (38 ± 11.4) versus 73 ± 13.3)] in the treated group compared with the placebo group.[11] Similar to our observation, they noticed no change in 25(OH)D levels between the third month and the final study visit (median of 96.5 versus 83 nmol/L, p=0.15), however, 16 of 20 children (80%) in their cohort achieved normal 25(OH)D levels after 3 months of intensive replacement treatment, whereas only 12 of 20 children (60%) had normal 25(OH)D levels after maintenance treatment (final study visit, p=0.06). Normal iPTH was required as an entry criterion in their study, and they monitored the use of ergocalciferol in children with vitamin D deficiency/insufficiency in preventing an increase in iPTH, and normalizing 1,25(OH)2D levels.

The patients in our cohort were already receiving alpha-calcidol, and they had high iPTH with vitamin D3 deficiency/insufficiency. In a previous study, we reported a negative correlation between 25(OH)D3 and iPTH in children with CKD who were on alpha-calcidol.[9] The addition of oral cholecalciferol in those children with low vitamin D3 levels did not improve the high iPTH. This could be explained by the low percentage of cases who achieved normal level; 11% compared to 80% in the study of Shroff et al,[11] in which higher doses were administered to children with more severe deficiency. We observed that the best response to treatment with oral vitamin D3 was in children with insufficiency, but it was worse than that reported by Shroff et al[11]. They reported a 100% response rate in children with stage 2 CKD compared with 2 out of 12 in our cohort (17%). This poor response could be explained by the rather low dose of vitamin D3 administered in our cases, but also by the non-adherence of the patients to therapy as reflected by the low percentage of children (27.7%) with vitamin D3 insufficiency who achieved normal levels, even though the KDOQI recommended dose of 2000 IU/day was prescribed. We did not measure C reactive protein in our cohort in order to exclude micro-inflammation as a cause of poor response to cholecalciferol, however, we measured ALP levels and these were within normal values for children. Serum ALP was reported to be associated with elevated CRP, and it was thought to be a marker of inflammation.[15]

Hari et al[16] from India reported a significant increase of vitamin D3 from 16.7 - 46.2 ng/mL, and improvement of PTH levels from 51.3 - 37.1 pg/ml (p=0.003) after 6 weeks of a single large dose (600,000 IU) of oral cholecalciferol. Rucker et al[17] from Canada reported a very high prevalence (93%) of vitamin D insufficiency/deficiency in adults with CKD living at northern latitudes. They also reported that daily oral vitamin D3 (1,000 IU/day) reduced vitamin D insufficiency by 37% compared with the 11% in our study. Moe et al[18] from USA demonstrated that daily low dose cholecalciferol (4000 IU/day for one month, then 2000 IU/day), or doxercalciferol (one microg/day) reduced PTH levels after 3 months in adults with CKD stages 3 and 4.

Our study showed that although there was some improvement in the levels of vitamin D3 in children who received oral vitamin D3, the iPTH levels were not affected as 25(OH)D3 levels did not normalize in most of the children. The non-adherence to treatment, which could explain our results, indicates that high initial doses might be advisable as was demonstrated by Hari et al[16]. Similar to previous studies, we did not observe hypercalcemia as a side effect of treatment with oral

cholecalciferol, and we did not measure urinary calcium excretion as we used low doses of the drug, which was shown to be safe in a previous study.[19] Similar to Hari et al[16] who demonstrated that high dose vitamin D3 is safe in children with CKD, Mallet et al[20] demonstrated that the administration of a single winter oral dose of 200,000 IU of vitamin D3 in adolescents in Normandy was safe and effective. Based on these findings, we propose that large doses of vitamin D3 be administered initially to normalize vitamin D3 levels and reduce iPTH, followed by maintenance daily oral doses. The other option is intermittent high doses of vitamin D3 as it was shown by Carnes et al[21] that 300 000 IU vitamin D3 orally 6-monthly may safely and effectively correct vitamin D deficiency in adolescents.

This study has some limitations. First, it is not a controlled study. Second, we did not measure 1,25 [OH]2D3 levels as we monitored RBD by measuring iPTH levels. Last, children who were not adherent to cholecalciferol were most likely also not adherent to alpha-calcidol.

In conclusion, the administration of oral vitamin D3 at doses of 2000 IU/day for 3-6 months in children with CKD resulted in improvement of their vitamin D3 levels, but had no effect on iPTH. Normal vitamin D3 levels were attained in a very small proportion of the patients. Large initial or intermittent doses of vitamin D3 might be more effective in normalizing vitamin D3 in children with CKD. Further studies on the effect of high intermittent doses on iPTH level, and compare it with the effect of low maintenance doses of vitamin D3 are warranted.

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