

# Vitamin D Status in Children with Chronic Kidney Disease

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## ABSTRACT

**BACKGROUND:** Vitamin D deficiency is a major contributor to secondary hyperparathyroidism in patients with chronic kidney disease (CKD). The objective of this study was to determine the vitamin D status in children with CKD.

**METHODS:** This cross-sectional study was conducted in the Department of Pediatric Nephrology, National Institute of Child Health (NICH), Karachi from January 2013 to December 2013. Ninety patients aged 3 months to 17 years with CKD were included. CKD was categorized into 5 stages based on glomerular filtration rate (GFR) and stage 4 and 5 were labeled as advanced CKD. Patients on 25-hydroxy vitamin D (25OHD) therapy were excluded. Radioimmunoassay was used to measure 25OHD level and it was defined as sufficient (>30-80 ng/ml), insufficient (16-30), mild to moderate deficiency (5-15 ng/ml) and severe deficiency (<5ng/ml). Data including age, gender, blood urea (U), serum creatinine (Cr), GFR, CKD-stage, etiology, serum calcium (Ca), serum phosphorus (P), serum alkaline phosphatase (ALP), serum parathyroid hormone (PTH) and serum 25OHD level were collected and analyzed

by SPSS using descriptive statistics.

**RESULTS:** Of the 90 patients, 55 (61.1%) were males. Mean age was 7.4± 4.6 years. Mean U, Cr and GFR were 113.5± 82.0 mg/dL, 3.9±3.4 mg/dL and 28.8±28.3 mL/min/1.73 m<sup>2</sup> respectively. Majority (66.7%) had advanced CKD and 44.4 % were undergoing dialysis. Etiologies of CKD were renal hypoplasia–dysplasia (36.6%), stone-disease (18.9%), posterior-urethral valves (16.7%) and juvenile-nephronophthisis (12.2%). Mean ± standard deviation of serum Ca was 8.3 ± 1.6 mg/dL, P 5.2±1.7 mg/dL, ALP 418.3±298 U/L and PTH 370.6±320.7 pg/ml. Mean 25OHD level was 18.9±16.8 ng/ml and its levels in males (17.73±10.63) and females (16.91 ± 9.74) were similar (p=0.79). Mean 25OHD level was suboptimal in 79 patients (87.8%); 37 (41.1%) had insufficiency, 33 (36.7%) had mild to moderate deficiency whereas 9 (10%) had severe 25OHD deficiency.

**CONCLUSION:** Vitamin D status was suboptimal in 87.8% of cases and 25OHD deficiency was severe in advanced CKD.

Keywords: Chronic kidney disease; 25OHD levels; Secondary hyperparathyroidism

## INTRODUCTION

Chronic kidney disease (CKD) is defined as an irreversible progressive renal damage lasting for three or more months [1, 2]. Reported prevalence of CKD in Pakistan varies from 12-29% of renal diseases in pediatric tertiary care centers [3, 4]. Patients with long standing CKD are at high risk of vitamin D deficiency (VDD) and it is a major contributor in the pathogenesis of secondary hyperparathyroidism (SHPT). SHPT in advanced stages of CKD is chiefly

attributed to deficiency of 1,25 dihydroxycholecalciferol {1, 25(OH)<sub>2</sub> D}, and combined with hyperphosphatemia, leads to disordered bone turnover and mineralization, known as mineral bone disorder (MBD). The dysregulated calcium (Ca), phosphorus (P), parathyroid hormone (PTH), and 25-hydroxyvitamin D (25OHD) along with increased fibroblast growth factor – 23 (FGF-23) result in vascular calcification which may contribute to high cardiovascular diseases and mortality both in children and adults[1,6-8].

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Recent evidence shows that vitamin D has other important biological functions such as modulation of immune system, endocrine system, and cardiovascular protection in addition to its classical function on bone and mineral metabolism [5]. VDD is common in children and its prevalence varies depending on multiple factors [9, 10–13]. Reported prevalence of VDD in CKD ranges from 20-80% depending upon the stage of CKD [9, 14]. Current clinical practice guidelines for management of CKD recommend evaluation for SHPT (serum Ca, P, ALP, PTH) and 25OHD if PTH is high followed by replacement with high dose vitamin D [15, 16]. This approach may delay the onset of secondary hyperparathyroidism. Current evidence shows that 25OHD is the major circulating form of vitamin D with half life of 2-3 weeks and its levels are the best indicator of vitamin D status [10–13]. Considering the important role of VDD in SHPT in children with CKD, this study was planned with the objective to determine the 25OHD levels in children with CKD.

## METHODS

This cross-sectional study on 90 children, aged 3 months to 17 years with CKD was carried out in the Department of Pediatric Nephrology, National Institute of Child Health (NICH), Karachi from January 2013 to December 2013 after approval from the Hospital Ethics Committee. Patients were enrolled after written/verbal informed consent from parents. National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-KDOQI) guidelines were used to classify CKD into 5 stages based on estimated glomerular filtration rate (GFR) as calculated by Schwartz formula [2, 15, 17]. CKD –stages were defined as stage 1= GFR > 90ml/min/1.73 m<sup>2</sup> (with evidence of renal damage), stage 2= GFR between 60-89 ml/min/1.73 m<sup>2</sup>, 3= GFR between 30-59 ml/min/1.73 m<sup>2</sup>, 4= GFR between =15-29 ml/min/1.73 m<sup>2</sup> and stage 5= GFR< 15 ml/min/1.73m<sup>2</sup>. Stage 4 and 5 are considered as advanced CKD. Patients with all CKD-stages 1-5 were included without consideration for the treatment modality (conservative or dialysis). Patients who were on vitamin D, 1- $\alpha$ -cholecalciferol were included while patients who were on 25OHD treatment were excluded from the study. Serum levels of 25OHD were measured at NICH laboratory by radioimmunoassay method. Vitamin D status was defined as sufficiency (>30-80 ng/ml), insufficiency

(16-30 ng/ml), mild to moderate deficiency (5-15ng/ml) and severe deficiency (<5ng/ml) [1, 15].

Data including age, gender, height and weight, serum Cr, GFR and CKD-stage, underlying etiology, mode of treatment (dialysis or conservative), bone biochemistry (Ca, P, ALP, PTH), 25OHD levels were collected and analyzed using Statistical Package for Social Sciences (SPSS) version 16. Categorical variables were summarized by frequencies and percentages while continuous variables were summarized with mean  $\pm$  SD. ANOVA was used to determine mean differences whereas chi-square was used for categories like gender and vitamin D status among CKD stages. Pearson correlation test was applied to observe the correlation between 25OHD levels with S. Cr, GFR, and bone biochemistry parameters. P <0.05 was taken as statistically significant.

## RESULTS

**Demographic Characteristics (Table 1):** Among the 90 patients, there was a male predominance (61.1%) with male to female ratio of 1.5:1. The mean age of study population was 7.4 $\pm$  4.6 years and common age groups (table 2) were 6-10 years (n=28, 31%) and above 10 years (n=27; 30%). The mean weight and height of patients was 16.8 $\pm$ 9.7 kg and 102.4 $\pm$ 29.4 cm respectively.

**Etiologies of CKD:** Renal hypoplasia –dysplasia was the most common etiology of CKD (33, 36.7%) followed by stone disease (17, 18.9%), posterior urethral valves (15, 16.7%) and juvenile nephronophthisis (11, 12.2%). Other causes of CKD were neurogenic bladder (7.8%), chronic glomerulonephritis (4.4%), reflux nephropathy (2.2%) and polycystic kidney disease (1.1%).

**Renal Function and Staging of CKD (Table 1):** The mean blood urea, serum Cr and GFR were 113.5 $\pm$ 82.0 mg/dL, 3.9 $\pm$ 3.4 mg/dL and 28.8 $\pm$ 28.3 ml/min/1.73 m<sup>2</sup> respectively. CKD stage 5 and 4 was observed in 34(37.8%) and 26(28.9%) patients respectively. Together both constitutes advanced CKD and accounts for 66.7% of all cases. Forty of the 90 (44.44%) patients were undergoing dialysis.

**Bone Biochemistry (Table 1):** Bone biochemistry showed mean serum Ca, phosphorus, ALP and PTH levels 8.3 $\pm$ 1.6 mg/dL, 5.2 $\pm$ 1.7 mg/dL, 418.3 $\pm$ 298.2 U/L and

**Table 1:** Demographics, biochemical parameters and vitamin D status in chronic kidney disease

Parameters		Stages of chronic kidney disease					
Demographics	Overall N=90	I (n=7)	II (n=3)	III (n=20)	IV (n=26)	V (n=34)	P value
Age( yrs)	7.4 ±4.6	6.6 ±3.7	6.0 ±2.6	6.2 ±4.4	6.7 ±4.4	9.0 ±5.1	0.182
Male	55 (61.1%)	4 (57.1%)	2 (66.7%)	12 (60%)	14 (53.8%)	23 (67.6%)	0.864
Female	35 (38.9%)	3 (42.9%)	1 (33.3%)	8 (40%)	12 (46.2%)	11 (32.4%)	
Wt(kg)	16.8 ±9.7	16.2 ±5.3	15.5 ±5.7	15.3 ±10.6	13.8 ±7.7	20.3 ±10.7	0.104
Ht(cm)	102.4 ±29.4	101 ±16.3	96.3 ±13.5	98.0 ±28.1	94.8 ±27.8	111.5 ±32.9	0.233
Biochemical Parameters							
Urea (mg/dl)	113.5 ±82.0	22.6 ±12.8	40.7 ±30.7	72.3 ±42.4	83.3 ±44.7	185.9 ±78.1	<0.001
SCr(mg/dl)	3.9 ±3.4	0.5 ±0.1	1.1 ±0.6	1.5 ±0.7	2.8 ±1.6	7.1 ±3.2	<0.001
GFR	28.8 ±28.3	108.4 ±13.8	71.9 ±5.8	37.3 ±9.4	21.4 ±9.2	9.3 ±3.6	<0.001
Ca (mg/dl)	8.3 ±1.6	9.3 ±0.7	9.4 ±0.7	8.7 ±1.3	8.5 ±1.5	7.7 ±1.9	0.034
P(mg/dl)	5.2 ±1.7	5.4 ±1.2	4.1 ±0.7	4.9 ±2.0	4.9 ±1.3	5.8 ±1.8	0.151
ALP (U/L)	418.3 ±298.2	291.0 ±76.8	287.3 ±111.1	397.4 ±337.5	431.1 ±260.9	458.6 ±337.2	0.632
PTH ( pg/ml)	370.6 ±320.7	89.7 ±118.7	115.8 ±144.9	226.7 ±252.8	424.3 ±309.9	494.6 ±332.6	0.001
Vitamin D Status							Total N (%)
25OHD (ng/ml)	18.9 ±16.8	21.8 ±12.9	18.1 ±5.4	25.6 ±12.4	21.4 ±26.2	12.4 ±6.7	0.056
Sufficiency	37.7 ± 9.9	2	0	5	3	1	11(12.22)
Insufficiency	20.9 ± 3.1	3	2	11	11	10	37(41.1)
Mild-moderate deficiency	10.6 ± 3.5	2	1	3	9	17	33(36.7)
Severe deficiency	4.3 ± 1.5	0	0	0	3	6	9(10)

S Cr= serum creatinine, GFR=estimated glomerular filtration rate ml/min/1.73m<sup>2</sup>, Ca= calcium, P= phosphorus, ALP=alkaline phosphatase, PTH= parathyroid hormone

370.6±320.7 ng/ml respectively.

**Vitamin D Status (Table 1):** The overall mean serum 25OHD level in patients with CKD was 18.9±16.8 ng/ml with a range of 1.6–54.4 ng/ml. The mean 25OHD levels in males were 17.7±10.6ng/ml compared to 16.9± 9.7 ng/ml in females. This difference (0.82) was not statistically significant (p=0.79). 25OHD levels were quite different (p=.002) being lowest (13.3±8.6ng/ml) in children above 10 years and below one years of age (Table 2). Of the 90 children, 37 (41.1%) had insufficiency, 33 (36.7%) had mild to moderate deficiency and 9 (10%) had severe 25OHD deficiency. Thus suboptimal levels of 25OHD (18.9±16.8 ng/ml) were observed in 79 cases (87.77 %) and in all the stages of CKD. It was noticeably low (6 out of 9) in CKD -stage 5 (Table 1 vitamin D status). Similarly high frequency of moderate VDD was also observed in CKD-stage 4 (9, 34.6%) and stage 5 (17, 50%). 25OHD level was also low in 14 patients (15.55%) receiving maintenance dose of 1-alfacalcidol. Pearson correlation revealed a weak direct correlation of 25OHD level with GFR (r=0.125, p=0.112) and indirect correlation

with serum Cr(r= -0.169, 0.242), both were not significant. Similarly there was no statistically significant relationship between 25OHD levels with serum Ca (r=0.09, P=0.410), serum P (r=-0.03, P=0.745), serum ALP (r= -0.10, P =0.325) and serum PTH (r = -0.04, P=0.69).

## DISCUSSION

We found a high prevalence (88%) of suboptimal

**Table 2:** Vitamin D level in children with chronic kidney disease according to age groups

Age Groups Mean ± SD= 7.4 ±4.6	N (%) =90	Vitamin D level Mean ±SD (ng/ml)
< 1 years	12 (13/3%)	14.7 ±7.2
1 – 5 years	23 (25.6%)	23.7 ±13.1
6 – 10 years	28 (31.1%)	22.1 ±25.1
> 10 years	27 (30%)	13.3 ±8.6

p- Value = 0.002

25OHD levels in children with CKD. Among 90 CKD patients, more than 41% had VD insufficiency, 37% had mild to moderate VDD and 10% presented with severe VDD. This is a first report from Pakistan in which we have documented the 25OHD levels in children with CKD. Similar studies have documented a high prevalence of VDD in children with CKD from many parts of World including India [9, 14, 18 – 21]. Reported prevalence of VDD in CKD children varies from 40-80% in a number of published studies, which is consistent with our findings [9, 14, 18]. The mean 25OHD levels ( $18.9 \pm 16.8$ ) in our study are comparable to a study by Ali FN et al in which it was 21.8 ng/ml [14].

A high frequency of severe VDD in children with advanced uremia (6 out of 9 with severe deficiency) is consistent with a study by Seehermvong W et al [19]. Kalkwarf H et al also found high frequency of VDD (26-74%) in CKD children compared to age matched healthy controls (31%) and this deficiency increased with the severity of CKD, 50 % in advanced CKD and 74% in patients on dialysis [18]. Although majority of patients (66.7%) in our study belonged to advanced CKD and some of them were on dialysis, the frequency of low levels of 25OHD was also high (71.4%) in early stage (CKD-stage 1) and in CKD stage 5(97.7%). Thus, our results are consistent with a study by Kalkwarf H et al [18].

In this study, we did not find significant changes in bone turnover markers (table 1) like hypocalcaemia ( $8.3 \pm 1.6$  mg/dl), hyperphosphatemia ( $5.2 \pm 1.7$  mg /dl), alkaline phosphatase ( $418.3 \pm 298.2$  U/L) and parathyroid hormone levels ( $370.6 \pm 320.2$  pg/ml). Our findings are consistent with the classical findings of secondary hyperparathyroidism in children with CKD [1, 6, 7]. Low 25OHD levels in advanced stages of CKD in the presence of classical bone turnover markers confirm the state of SHPT, which is also consistent with other studies [9, 15, 18].

Vitamin D supplementation may suppress the PTH synthesis and prevent development of SHPT and its associated consequences [6 – 8, 18, 19, 21]. Low 25OH levels in children receiving alfacalcidol in more than 15% in this study suggest that nutritional form of VD is necessary for extra-renal conversion of 25OHD to 1,25hydroxycholecalciferol. Current guidelines recommend measurement of 25OHD in CKD stage 2-4 if PTH is high [15]. We suggest, based on the findings in our study, that these guidelines

may be modified as 25OHD levels should be measured in all stages of CKD and supplementation of VD in all patients with suboptimal levels ( $<30$  ng/ml). This strategy may delay the onset of secondary hyperparathyroidism [21].

There are certain confounding factors such as vitamin D intake in diet, medications and sunlight exposure which affect 25OHD levels, however, this study did not measure these variables and we cannot examine the effect of these confounding variables on the outcomes. Further, as there was no control group without CKD, we cannot conclude with certainty that the prevalence of vitamin D deficiency is higher in CKD children than children without CKD.

## CONCLUSION

In this study, a high frequency (87.8%) of suboptimal vitamin D levels suggest that 25OHD levels should be measured in all stages of CKD and fortification strategy of vitamin D may be implemented.

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