


Vitamin D Deficiency in Children with Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) and Factors Affecting Response to Cholecalciferol Therapy: A Quasi-Experimental Study from Low-Middle Income Setting

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ABSTRACT

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Background and Objective: Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) is characterized by hypocalcemia, hyperphosphatemia and abnormal vitamin D (VD) metabolism resulting in high parathyroid hormone secretion. The objective of the study was to determine VD status in children with CKD-MBD and the effect of cholecalciferol therapy in these children.

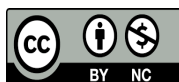
Methods: This quasi-experimental study was conducted at the Department of Pediatrics, National Institute of Child Health, (NICH), Karachi, during 2016-2017. The sample size was 81. VD deficient and insufficient patients were supplemented with oral cholecalciferol and response was assessed by vitamin D (25-OHD), serum calcium, phosphorus and parathyroid hormone (PTH) levels after 3 months.

Findings: Fifty (61.70%) were males and 31(38.30%) females. The mean age was 8.06 ± 4.01 years with a majority (70.37%) above 5 years. The mean height was 125.85 ± 25.38 centimeters. The mean disease duration was 2.37 ± 1.38 years. The majority of patients had CKD stage III (56.80%), followed by stage IV (24.7%) and stage II (18.5%). Most patients were insufficient (85.2%) and others were deficient (14.8%) in VD status. The mean serum 25-OHD, PTH, Calcium and Phosphorus levels before therapy and after supplementation were 16.98 ± 4.24 ng/ml and 39.34 ± 9.08 ng/ml, 105.11 ± 26.40 pg/ml and 90.82 ± 24.92 pg/ml, 8.92 ± 0.77 mg/dl and 9.32 ± 0.76 mg/dl, 3.61 ± 0.37 mg/dl and 4.07 ± 0.38 mg/dl, respectively. The P-value was <0.05 .

Conclusion: VD supplementation has increased serum calcium and serum 25-OHD levels and suppressed phosphate and PTH levels which may halt the MBD and thereby improve the outcome of CKD. Therefore, early supplementation with cholecalciferol therapy is recommended for all children with CKD.

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Introduction

Chronic kidney disease (CKD) is defined as “structural or functional kidney damage that persists over a minimum of three months”. Functional damage is defined by the decline of estimated glomerular filtration rate (eGFR), a persistent rise of urinary protein excretion, or both [1].

The overall prevalence of CKD throughout the globe is estimated to be around 8-16% [2]. Although disease prevalence in children is relatively lower as compared to adults, its incidence is gradually increasing, with a global annual incidence rate of 8% [3]. As adults, many of the comorbid conditions are seen in children that hamper their lifestyle very badly including cardiovascular, bone disease and cognitive impairment. By the end of the 2nd decade of their life, a notable percentage of pediatric patients with CKD progress to renal failure. This significantly impairs their quality of life along with increased mortality risk [4]. Age-specific prevalence of CKD among the Pakistani population shows that younger ones (aged less than 30 years) have the lowest prevalence (10.5%) as compared to the elderly population (43.6% among 50 or more years old) [5]. Data from Pakistan indicate that CKD accounts for around 10-12% of all renal cases in children but its exact prevalence and incidence are not known [6].

As per the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, CKD is categorized into five stages, based on eGFR, stage 5 being the most severe and stage 1 the least severe [7]. CKD-MBD indicates changes in mineral and bone metabolism due to falling GFR in CKD. These changes start as soon as the GFR starts declining but becomes more obvious once eGFR falls below 60ml/min/1.73m² [2]. Changes in mineral and bone metabolism in CKD-MBD lead to increased bone turnover and decreased bone mineralization leading to decreased bone volume. The mechanism of these morphological changes is low vitamin D level which leads to hypocalcemia leading to parathyroid hormone (PTH) secretion, which stimulates bone turnover to release calcium and phosphorus to maintain their homeostasis. Increased bone turnover leads to an increase in bone alkaline phosphatase released by active bone cells (osteoblasts) [8].

Under the effect of ultraviolet radiation, cholesterol in human skin is converted to vitamin D after a series of chemical reactions. Whether endogenously produced or taken in the diet, the inactive form of vitamin D is transported to the liver, where the 25-hydroxylase enzyme metabolizes it to yield 25-hydroxyvitamin D [25(OH) D]. This form of vitamin D is measured to assess an individual's vitamin D status, as it is the prime storage source of vitamin D and has ½ life of around 20 days [9]. This, still biologically inactive form, is further converted to 1, 25-dihydroxy vitamin D [1, 25(OH) 2D] by another hydroxylase enzyme located mainly within the proximal tubules of the kidneys i.e. 1- α -hydroxylase. This active form of vitamin D has ½ life of only 10 hours and is affected by multiple factors like changes in parathyroid hormone (PTH), calcium, phosphorus and fibroblast growth factor 23 (FGF 23) levels, therefore it is not considered as a good indicator of vitamin D status of a patient [10].

Multiple factors are responsible for the deficiency of 25 (OH) D in children with CKD [11]. Major reasons are the inadequate intake of vitamin D and calcium-containing foods along with limited sun exposure due to a decrease in outdoor physical activity. Studies have found that children with CKD have a blunted response to sunlight. Due to some unidentified factors/mechanisms, these children were found to be unable to convert provitamin D3 to vitamin D3 despite adequate concentrations of the latter [12]. In patients with proteinuric CKD, urinary loss of vitamin D binding protein is another cause of vitamin D deficiency [13, 14]. Hyperphosphatemia and hypocalcemia due to compromised renal functions and decreased activation of vitamin D by failing proximal renal tubules lead to increased secretion of parathyroid hormone, leading to secondary hyperparathyroidism (SHPT). This SHPT further worsens the deficiency of 25 (OH) D by increasing the activity of 24 hydroxylase enzymes which increases the degradation of 25 (OH) D [15].

Hyperphosphatemia and increased level of FGF-23 causing downregulation of 1- α hydroxylase is the main factor responsible for the loss of the kidney's ability to convert 25 (OH)D to

1,25(OH)₂D. Acidosis and uremia suppress the actions of 1- α hydroxylase [16]. A surface protein called Megalin is required by the kidneys for endocytosis of the 25 (OH) D-VDBP complex from the glomerular ultrafiltrate to the 1- α hydroxylase enzyme in the proximal tubule. Megalin expression is reduced in CKD thereby further adding to 1, 25(OH) 2D deficiency [17].

Previous Kidney Disease Outcome Quality Initiative (KDOQI) guidelines recommended that if PTH levels were found higher than the target levels for a specific stage of CKD, only then the vitamin D level should be measured in stage 3 and 4 CKD. The most recent KDOQI and the KDIGO guidelines recommend that 25(OH) D should be measured in all children with CKD stage 2-5, at least once a year [18, 19]. Supplementation is initiated if the levels are <30 ng/ml [20]. KDOQI guidelines do not make a distinction between using ergocalciferol (D2) vs. cholecalciferol (D3) as there is insufficient data to prove the superiority of one over the other [21].

The current study was designed to determine the effect of cholecalciferol therapy in vitamin D deficient and insufficient children with CKD and also find out whether this response was affected by the gender, age, weight and initial height of the patient, stage of CKD and duration of illness. All this will help us to develop preventive and treatment strategies for our patients so that consequences to CKD-MBD can be avoided.

Methods

Design and Participant

This quasi-experimental study was conducted at the Department of Pediatrics, National Institute of Child Health, (NICH), Karachi, during 2016-2017. The study was given approval by the Ethical Review Committee of NICH under the code NICH-ERC-024/04-2016. All children aged 6 months to 15 years of either gender with CKD Stage 2-4 were included. Stages of CKD were defined as per KDOQI guidelines that are based on GFR. CKD stage 2 was labeled if GFR was 60 to 89 ml/min/1.73 m², stage 3 if GFR was 30 to 59

ml/min/1.73 m² and stage 4 if GFR was 15 to 29 ml/min/1.73 m² [22]. Patients who met the inclusion criteria were enrolled in the study after informed consent. Patient/parents' confidentiality was ensured.

Patients who received either oral or injectable vitamin D during the last 3 months were excluded as the patients with CKD stage 5/ESRD were referred to other institutes for renal transplant or continuous renal replacement therapy and were given calcitriol rather than inactive form. Patients with very high levels of serum phosphate were also excluded since they needed other treatments along with using vitamin D supplements.

Sampling and sample size

Non-probability consecutive sampling technique was used for the study. After taking a confidence level of 95%, power of 80%, Phosphorus level increased from 3.7 ± 0.4 at baseline to 3.9 ± 0.5 mg/dl, [23] the estimated sample size was small, but in the present study, at least 81 vitamin D deficient and insufficient children with CKD were selected.

Intervention

In this study, vitamin D sufficiency, insufficiency and deficiency were labeled as per the KDOQI guidelines. When vitamin D level was >30 ng/ml, 16-30 ng/ml and <15 ng/ml, sufficiency, insufficiency and deficiency were labeled, respectively. Vitamin D deficiency was further classified as severe deficiency if levels were <5 ng/ml and mild deficiency if levels were 5-15 ng/ml [22]. Oral cholecalciferol supplementation was given to all patients with vitamin D insufficiency and deficiency as per the pediatric KDOQI guidelines (table 1) [24]. Cholecalciferol therapy was prescribed by the pediatric nephrologist who was also a member of the research team. Chewable D-max 2000 IU tablets by Matrix Pharma were used and if the dose was low or the patient was unable to take these chewable tablets, then, D-max drops 400IU, by the same pharmaceutical company were given. All patients received the same brand of medications.

Table 1. Recommendations for vitamin D supplementation in children with CKD stages 2 to 4 as per the pediatric KDOQI guidelines

Serum 25 (OH) D (ng/ml)	Definition	Dose of ergocalciferol/cholecalciferol	Duration
<5	Severe 25(OH)D deficiency	8,000 IU/day orally (or 50,000 IU/week) for 4 weeks; followed by 4,000 IU/day orally (or 50,000 IU twice monthly) for 2 months	3 months
5–15	Mild 25(OH)D deficiency	4,000 IU/day orally (or 50,000 IU every other week) for 12 weeks	3 months
16–30	25 (OH)D insufficiency	2,000 IU/day orally (or 50,000 IU every 4 weekly)	3 months

Evaluation of Biochemical parameters

Biochemical parameters like vitamin D, serum calcium, serum PTH and serum phosphate levels were measured before and after 3 months of the treatment. Each patient was followed by a specified team member till the collection of after-treatment blood samples. The DIASource 25OH Vitamin D Total ELISA strip reader machine was used to measure the vitamin D levels by manual ELISA method. Serum calcium and phosphorus were measured using the Microlab300 chemistry analyzer machine by the ELITech group, USA. Parathyroid hormone was measured by a full automation machine i.e. complete automatic chemistry analyzer.

Statistical analysis

Data were collected on pre-designed proforma and analyzed on SPSS version 17. Mean \pm SD were calculated for age, height, duration of disease, pre and post vitamin D level, PTH level, serum calcium and serum phosphate levels. Frequency and percentage were calculated for gender, vitamin D status, and phases of CKD. Paired t-test was applied to compare vitamin D, PTH level, serum calcium and serum phosphate levels before and after treatment. Stratification was done for age, gender, height and duration of disease to control the effect modifier. A post-stratification paired t-test was applied. P-value <0.05 was taken as significant.

Results

Total 81 children of both genders, aged 6 months-15 years meeting inclusion criteria of the

study were evaluated to determine the response of cholecalciferol in vitamin D deficient and insufficient children with CKD.

In the current study, males were predominant with the ratio of 1.7:1, and the majority of patients were >5 years of age. Stage III CKD was observed most commonly in the present study, followed by stage IV and stage II, respectively. The ongoing study revealed that 85.2% were insufficient and 14.8% were deficient in vitamin D status (table 2).

The mean age was 8.06 \pm 4.01 years with a minimum age of 2 years and a maximum of 15 years. Moreover, the median and range statistics were applied for age. Descriptive statistics for height were applied in the present study, and the mean height \pm SD was 125.85 \pm 25.38 centimeters. The mean disease duration was 2.37 \pm 1.38 years with a minimum duration of one year and a maximum duration of 5 years. Besides, median and range statistical descriptions were also calculated for disease duration (table 3).

In this study, all CKD parameters improved significantly after treatment with vitamin D. Serum 25(OH) D levels increased significantly and calcium and phosphate levels also normalized with significant suppression of PTH (table 4). In the present study, cholecalciferol therapy was found very effective in improving serum 25(OH) D, calcium and phosphate levels and suppressing PTH levels in patients of all ages and both genders with any weight and initial height. This effect was found in CKD of all stages and any duration (table 5).

Paired t-test was applied to compare vitamin D, PTH, serum calcium and serum phosphate levels before and after treatment. In addition, paired t-test

was applied for gender, age, weight, height, CKD duration and CKD stages to compare vitamin D, PTH, serum calcium and serum phosphate levels before and after treatment.

Discussion

There is growing recognition of the role of vitamin D on the innate immune system to prevent infections and the adaptive immune system to modulate autoimmunity [7]. Studies have reported that CKD is characterized by low 25 (OH) vitamin D (calcidiol), low 1, 25(OH)₂ vitamin D (calcitriol) as well as vitamin D resistance [8]. Alterations related to vitamin D metabolism, hyperphosphatemia and hypocalcemia lead to increased synthesis and/or secretion of PTH leading to secondary hyperparathyroidism (SHPT) that sets as soon as GFR falls below 60 ml min⁻¹ [8, 25].

The current study was conducted to determine the response of cholecalciferol in vitamin D deficient and insufficient children with CKD. In the present study, the response of cholecalciferol therapy was significant. Vitamin D supplementation was found to suppress the PTH synthesis and prevent the

development of SHPT and its associated consequences [26, 27].

In the ongoing study, the vitamin D insufficiency and deficiency were 85.2% and 14.8%, respectively, which is comparable with that of Moorani KN et al. who found an 88% prevalence of suboptimal 25-(OH)D levels in CKD children from Pakistan [28]. Similar studies have documented a high prevalence of vitamin D deficiency in children with CKD from many parts of the world including India [9, 10, 29-32]. But these results are quite higher as compared to international data. Stein D. R. et al. reported that among 100 American children with CKD, 16% were deficient in 25-(OH)D (≤ 20 ng/mL) and another 24%, insufficient (≤ 30 ng/mL) with 40% in the suboptimal range [33]. Besides, our results are inconsistent with the results of Abdulaziz Kari J. et al. in Saudi Arabia, who reported that among 80 children with CKD, only 10 children (12.5%) had normal vitamin D levels while the remaining 36 (45.0%) had vitamin D insufficiency, 34 (42.5%) had vitamin D deficiency. This may be because of other factors like lack of proper nutrition and lack of easy and early availability of health facilities in our setup [34].

Table 2. Frequency of patients according to age, gender, CKD stage and vitamin D Status (n=81)

Variables		Frequency (%)
Age group (years)	Age \leq 5 years	24 (29.63)
	Age > 5 years	57 (70.37)
Gender	Male	50 (61.70)
	Female	31 (38.30)
Stage of CKD	Stage II	15 (18.5)
	Stage III	46 (56.8)
	Stage IV	20 (24.7)
Vitamin D status	Insufficient (%)	69 (85.2)
	Deficiency (%)	12 (14.8)

Table 3. Descriptive statistics of age (years), height (cm) and disease duration (years) (n=81)

Descriptive Statistic	Mean \pm SD	Median	Minimum	Maximum	Range
Age (Years)	8.06 \pm 4.01	8	2	15	13
Height (cm)	125.85 \pm 25.38	132.3	74.4	168.2	93.8
Disease duration (Years)	2.37 \pm 1.38	2	1	5	4

Table 4. Comparison of serum 25-(OH) D level and bone biochemistry before and after treatment (n=81)

Variables	Serum 25-(OH)D level (ng/ml)		PTH level (pg/ml)		Serum Phosphate level (mg/dl)		Serum Calcium level (mg/dl)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	16.98	4.24	105.11	26.4	3.61	0.37	8.92	0.77
After treatment	39.34	9.08	90.82	24.92	4.07	0.38	9.32	0.76
p-value	<0.05		<0.05		<0.05		<0.05	

Table 5. Comparison of serum 25-OHD levels and bone biochemistry before and after treatment according to gender, age, height, weight of the patient, CKD stage and CKD duration

Variables			Serum Phosphate (mg/dl)		Serum Calcium (mg/dl)		PTH Level (pg/ml)		Serum 25-(OH)D Level (ng/ml)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gender	Male (n=50)	Baseline	4.07	0.37	8.94	0.69	102.44	26.91	17.5	3.94
		After Treatment	3.61	0.39	9.34	0.66	88.36	25.32	39.44	8.99
		P-Value	<0.05*		<0.05*		<0.05*		<0.05*	
	Female (n=31)	Baseline	3.62	0.38	8.9	0.89	109.41	25.38	16.16	4.64
		After Treatment	4.07	0.36	9.28	0.91	94.8	24.15	39.19	9.37
		P-Value	<0.05*		<0.05*		<0.05*		<0.05*	
Age of patient	≤5 years (n=27)	Baseline	3.48	0.35	8.96	0.81	100.6	24.47	15.25	3.66
		After Treatment	3.96	0.38	9.35	0.76	86.55	23.41	39.14	9.61
		P-Value	<0.05*		<0.05*		<0.05*		<0.05*	
	>5 years (n=54)	Baseline	3.68	0.36	8.9	0.75	107.4	27.25	17.85	4.28
		After Treatment	4.12	0.37	9.31	0.77	92.96	25.59	39.44	8.9
		P-Value	<0.05*		<0.05*		<0.05*		<0.05*	
Height of patient	≤125 cm (n=33)	Baseline	3.48	0.33	8.9	0.78	100.8	24.45	15.84	3.63
		After Treatment	3.95	0.35	9.28	0.76	86.45	22.87	39.33	9.52
		P-Value	<0.05*		<0.05*		<0.05*		<0.05*	
	>125 cm (n=48)	Baseline	3.71	0.37	8.94	0.77	108.1	27.51	17.77	4.49
		After Treatment	4.15	0.38	9.35	0.77	93.83	26.05	39.35	8.87
		P-Value	<0.05*		<0.05*		<0.05*		<0.05*	
Weight of patient	≤30 kg (n=41)	Baseline	3.52	0.36	8.89	0.36	99.9	22.84	16.43	3.7
		After Treatment	3.98	0.37	9.28	0.77	85.75	21.51	38	10.11
		P-Value	<0.05*		<0.05*		<0.05*		<0.05*	
	>30 kg (n=40)	Baseline	3.72	0.36	8.96	0.76	110.5	28.92	17.55	4.72
		After Treatment	4.16	0.37	9.36	0.76	96.02	27.29	40.72	7.78
		P-Value	<0.05*		<0.05*		<0.05*		<0.05*	
CKD STAGE	Stage II	Baseline	3.53	0.38	9.2	0.65	107.3	22.42	16.73	3.43
		After treatment	3.96	0.37	9.58	0.6	95.6	22.74	41.4	10.52
		p-value	<0.05*		<0.05*		<0.05*		<0.05*	
	Stage III	Baseline	3.61	0.38	8.81	0.68	103	27.66	17.17	4.56
		After treatment	4.06	0.37	9.23	0.71	87.71	25.44	37.08	7.15
		p-value	<0.05*		<0.05*		<0.05*		<0.05*	
CKD Duration	Stage IV	Baseline	3.7	0.34	8.97	0.99	108.3	26.95	16.75	4.21
		After treatment	4.18	0.38	9.33	0.96	94.4	25.44	43	10.71
		p-value	<0.05*		<0.05*		<0.05*		<0.05*	
	≤3 years (n=61)	Baseline	3.59	0.37	8.94	0.77	103.5	26.35	16.73	4.22
		After Treatment	4.05	0.37	9.34	0.75	89.47	24.98	39.39	9.7
		P-Value	<0.05*		<0.05*		<0.05*		<0.05*	
	>3 years (n=20)	Baseline	3.7	0.36	8.87	0.79	110	26.61	17.75	4.33
		After Treatment	4.14	0.39	9.27	0.82	94.95	24.94	39.2	7.08
		P-Value	<0.05*		<0.05*		<0.05*		<0.05*	

*P-value ≤0.05 is considered a significant level.

In the ongoing study, mean serum 25-(OH) D levels were significantly low with elevated mean PTH levels. The mean serum calcium levels were at a lower normal level with mean serum phosphate levels in the slightly upper normal range, which are consistent with the findings of SHPT in CKD children in other studies [25, 32]. Low 25- OH D levels in advanced stages of CKD in the presence of

classical bone turnover markers confirmed the state of SHPT, which is compatible with the results of other studies [35- 37]. Unlike Moorani KN et al., Belostotsky et al. [10] and Wesseling K et al. [38] reported that there were no significant changes in bone turnover markers like hypocalcaemia (8.3±1.6mg/dl), hyperphosphatemia (5.2±1.7mg/dl)

and parathyroid hormone levels (370.6 ± 320.2 pg/ml) [28].

The present study revealed that all CKD parameters improved significantly, as compared to baseline, after cholecalciferol therapy, mean serum 25-(OH)D and mean serum calcium levels significantly increased slightly but acceptable increase in mean serum phosphate levels. The mean PTH level was significantly decreased after therapy. All these are matching with Moe SM et al.'s findings, who stated that in the group receiving cholecalciferol, 25(OH) D levels increased from a baseline mean of 14.0 ± 6.1 to 37.1 ± 10.1 ng/mL, intact PTH decreased from a baseline 109 ± 43 to 97 ± 49 pg/ml, phosphorus level increased from a baseline, 3.7 ± 0.4 to 3.9 ± 0.5 mg/dl and calcium level increased from a baseline 9.0 ± 0.8 to 9.0 ± 0.6 mg/dl at study completion [24].

In the current study, males were predominant with a ratio of 1.7:1. CKD is more common in males than female children because of the higher frequency of congenital abnormalities of the kidney and urinary tract (CAKUT) in males. The most observed CKD stage was stage III followed by stage IV and stage II.

Moreover, we studied less commonly discussed factors in literature in terms of treatment response. In the current study, it was observed that patients of all stages of CKD and any duration of illness responded very well with vitamin D supplementation. Serum 25-(OH) D levels and serum calcium levels increased significantly with improvement in serum phosphate levels and suppression of PTH levels after treatment with vitamin D supplements. Further, the patient's gender, age at the time of diagnosis, weight and initial height of disease had no more effects on the treatment results.

Strengths and Limitations of the Study

All patients of this prospective study were followed for 3 months. All patients enrolled in the study received Vitamin D from the same manufacturer and all lab tests were done with the same company machines. The ongoing study discussed cholecalciferol therapy response in CKD children against less focused factors in the literature

like initial height and weight of the patient to find whether they had any effect on treatment. The limitations of the present study included a single-center experience, low female representation and nonrandomized study design. It was conducted with small sample size and in an urban environment; therefore, the results might not be generalizable to larger populations.

Conclusion

During this study, it was found that a large proportion of CKD children were either Vitamin D deficient or insufficient. Cholecalciferol therapy was found effective in suppressing SHPT and improving parameters of mineral bone disease in CKD. Initial supplementation with vitamin D increased serum calcium and serum 25- OH D levels along with suppressing serum phosphate and PTH levels. Suppressing the PTH levels led to decreasing/slowing down the process of mineral bone disease and thereby improving the outcome and decreasing morbidity and mortality in CKD children. Hence, it is recommended that cholecalciferol therapy should be started early in the disease irrespective of the stage of CKD, duration of illness, age of the patient and initial height of the patient.

Suggestion

It is recommended that all CKD patients should be treated with Vitamin D supplements irrespective of the disease stage, duration and socio-demographic factors of the patient like initial height, weight and age of the patient to prevent SHPT and mineral bone disease.

Ethical approval

Informed consent was obtained from parents. This study was approved by an Ethical Review Committee of the National Institute of Child Health Karachi. The study was given approval by the Ethical Review Committee of NICH under the code NICH-ERC-024/04-2016

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Conflict of interest

The authors declare that there is no conflict of interest.

Availability of data and materials

Most of the data generated or analyzed during this study are included in this article. Limited data can be provided in person on request to the main author.

Authors' contributions

AK was the main author who collected data from children's parents/guardians regarding illness and advised cholecalciferol therapy, depending on the severity of vitamin D deficiency/insufficiency. AJ analyzed and interpreted that data along with help in writing the manuscript. KM helped in study design and was the main supervisor throughout study, analysis and manuscript writing. SF helped in collecting and analyzing data. AJ was the main statistician and research analyst for the interpretation of results. All authors read and approved the final manuscript.

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