Vitamin D Deficiency and Parathyroid Response in Critically-ill Children: Association with Illness Severity and Clinical Outcomes

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Objective: To determine the prevalence of vitamin D deficiency in critically ill children, and to study its association with parathyroid response, severity of illness and clinical outcomes.

Design: Prospective observational study.

Setting: Medical Pediatric Intensive Care Unit of a tertiary care centre of Northern India.

Participants: 154 children in-patients: August 2011-January 2013.

Main outcome measures: Vitamin D deficient children were (serum 25-hydroxy vitamin D <20 μg/mL) divided into "parathyroid-responder" [serum parathyroid hormone >65 pg/mL with 25(OH)D<20 μg/mL and/or calcium corrected for albumin <8.5 mg/dL] and "non parathyroid-responder." Illness severity was assessed by Pediatric Index of Mortality-2 (PIM-2) score at admission. Biochemical parameters, illness severity scores and clinical outcomes were compared between parathyroid-responders and non-parathyroid-responders.

Results: Vitamin D deficiency and hypocalcemia were observed in 125 (83.1%) and 91 (59%) children, respectively at admission. There were no differences in illness severity score at admission, mortality rate and length of stay between vitamin D-deficient children and 19.8% of non-vitamin D-deficient children. Among Vitamin D-deficient children, parathyroid-responders had higher PIM-2 score at admission compared to non-parathyroid-responder [12.8 (7.4,20.6) *vs.* 6.5 (2.5,12.2), *P*=0.01]. However, there were no differences in other clinical outcomes between two groups.

Conclusion: Critically ill children have high prevalence of vitamin D deficiency. Parathyroid gland response secondary to hypocalcemia or vitamin D defiency is impaired in critical illness.

Keywords: *Calcium, Illness severity, Outcome.*

The pleiotropic action of vitamin D plays a central role in the critical illness pathophysiology. Vitamin D receptor is found in B and T lymphocytes, bone marrow and cardiac cells, and there is growing evidence regarding its cardio-protective, immunomodulatory and antimicrobial properties [1]. Studies have documented higher prevalence of vitamin D deficiency in critical care settings [2-6]. Whether this deficiency is associated with severity of illness or other clinical outcomes is unclear [10].

We hypothesized that there is impairment in the Calcium—Parathyroid hormone (PTH)–Vitamin D axis due to critical illness. Assessing vitamin D deficiency in terms of PTH response and its association with illness severity and clinical outcomes is necessary to get insight for further interventional studies for optimizing the management of Vitamin D deficiency, particularly in the setting where vitamin D deficiency is highly prevalent even in healthy children. We, therefore, conducted this study to determine the prevalence of Vitamin D deficiency and characterize its relation with calcium and PTH, and assess the outcome considering type of parathyroid response in vitamin D-deficient children.

METHODS

This was a prospective cohort study conducted in Pediatric Intensive Care Unit (PICU) of All India Institute of Medical Sciences, New Delhi, India, and was a secondary objective of data collected as a part of 'Hypophosphatemia in Pediatric Critical Illness' study by the same group. In this study, all the children aged between 1 month and 15 years were eligible for inclusion. Exclusion criteria were: known parathyroid disease, rickets, renal tubular acidosis, chronic kidney disease (CKD) diagnosis of acute kidney injury (AKI) at admission. Children requiring readmission and those who died within 24 hours were also excluded. Ethical approval was obtained from Institutional ethics committee. Parents of the children fulfilling the criteria were approached for the written informed consent for the participation of the child in the study.

The following variables were recorded at baseline for each patient: age, gender, season of admission, vitamin D supplementation, type of milk-product consumption, anthropometry, and documentation of underlying chronic illness if any. Pediatric Index of Mortality 2 (PIM2) score was used to assess illness severity at admission [11]. Serum 25(OH)D, PTH, total calcium, alkaline phosphatase (ALP), albumin and phosphate levels were measured at admission, preferably within 24 hours. Children did not receive any form of Vitamin D supplementation prior to blood sampling. Children were followed-up throughout the PICU stay. Evidence of sepsis, septic shock, acute respiratory distress syndrome (ARDS), need for mechanical ventilation, duration of mechanical ventilation, need for renal replacement therapy (RRT), duration of PICU stay and mortality were recorded. Other standard and relevant investigations (blood culture, blood gas, electrolytes, kidney function test, etc) were recorded at the time of admission.

Patients with vitamin D level less than 20 ng/mL were categorized as deficient [12-14]. Secondary hyperparathyroidism was defined as a serum PTH level >65 pg/mL, corresponding to the upper limit of the laboratory reference range [15]. Hypocalcemia was defined as total serum calcium (corrected for albumin) <8.5 mg/dL [16]. To evaluate parathyroid hormone response in the setting of hypocalcemia or hypovitaminosis D, children were classified to have "adequate PTH response/PTH responder" or "inadequate PTH response/PTH non-responder". PTH-responders were defined as patients who had PTH >65 pg/mL together with 25(OH)D <20 ng/mL and/or total calcium corrected for albumin <8.5 mg/dL based on measurements made at the time of PICU admission. Malnutrition was defined as weight-for-age Z-score < -2 for children up to 10 years and BMI-for-age Z-score < -2 for children above 10 years as per World Health Organization (WHO) growth chart and WHO reference [17]. Sepsis and septic shock were defined according to the International Pediatric Sepsis Consensus Conference criteria [18]. Acute kidney Injury (AKI) was defined based on either urine output or serum creatinine criteria [19]. ARDS was defined using standard definition [20].

Illness severity and various clinical outcomes were compared between children having vitamin D deficiency and those not having vitamin D deficiency. Those children with vitamin D deficiency and secondary hyperparathyroidism were classified as 'PTH responder'. Proportion of vitamin D deficient children showing adequate PTH response was calculated. Illness severity score and various clinical outcomes were assessed between PTH responder and non-PTH responder in vitamin D deficient children.

Blood samples were transported in ice pack immediately after collection for cold centrifugation and plasma separation. Separated plasma samples were stored at -80^0 C, and were analyzed for 25(OH)D and PTH values in batches, every 2-weekly. Serum 25(OH)D was assayed by an auto-analyzer (DiaSorin Liaison, Italy) using a chemiluminescent tracer, with a measuring range of 4 to 150 ng/mL (inter- and intra-assay coefficient of variation of 10%). Serum PTH level was estimated by using electrochemiluminometric assay using a Cobas e411 auto analyzer (Roche Diagnostics, Basel, Switzerland), with a measuring range of 1.2 to 5000 pg/mL. Serum calcium, phosphorus, and ALP were estimated by colorimetric method using a Beckman Coulter Synchron-CX9 PRO clinical system (Beckman Coulter, Inc).

Statistical analysis: Data were analyzed using STATA 11 software (Stata Corp, College Station, TX). Differences between groups were assessed using the chi-square test for categorical variables and Student's t-test or Wilcoxon ranked sum test for continuous variables, depending on the distribution of variables. Correlation coefficients were calculated using Spearman's rank correlation. A P value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 162 children out of 295 admissions met inclusion criteria. Most common reasons for exclusion were: AKI (30), CKD (27), readmission (26), transfer out within 24 hour (18), death within 24 hour (16) and refusal of consent (16). Serum PTH and vitamin D estimation could not be done in 8 children, and thus 154 children were included in analysis. The general characteristics of study population are shown in *Table* **1**. The most frequent causes of admission were Acute respiratory infection (16.8%), tropical infectious disease (15.6%) like dengue, malaria, etc., central nervous system disease (15.6%), congenital heart disease (9.1%), liver disease (9.7%), genetic disorder (6.5%), gastrointestinal disorders (5.8%), rheumatologic disorders (5.8%), and others (15%). No child received any form of vitamin D supplementation prior to admission. Around 56% of children had some underlying chronic illness.

The prevalence of vitamin D deficiency [25(OH) D <20 ng/mL] was 83.1% (95% CI 77.1, 89.0). Fourteen out of 154 children (9.1%) had 25(OH)D levels between 20 to 29.9 ng/mL. Only 7.8% of children had 25(OH) D ≥30 ng/mL. Twenty-one children (13.6%) had 25(OH)D less than 5 ng/mL. Hypocalcemia was common in Vitamin D deficient group. Serum calcium corrected for albumin was lower in vitamin D deficient group compared to non-deficient group (*P*=0.02). Median PTH value was higher in vitamin D

TABLE I DEMOGRAPHIC, CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF STUDY POPULATION (*N*=154)

Characteristics	Value
Age (mo)	30 (6-102)
Weight (kg)	10 (5.2-19.7)
Malnutrition, *n* (%)	101 (65.6)
Male gender, *n* (%)	102 (66.2)
PIM2 score	7.2 (2.8-14.5)
Need for mechanical ventilation, *n* (%)	109 (70.8)
PICU length of stay	7 (3-16)
Duration of ventilation	8 (3-15)
Serum 25(OH)D, ng/dL	11.7 (7.1- 16.0)
PTH, pg/mL	33.7 (17.8-56.7)
Calcium corrected for albumin, mg/dL	8.2 (7.4-9.0)
Serum phosphate, mg/dL	3.7 (2.9-4.4)
Serum ALP, IU/mL	428 (296-604)

PIM2: Pediatric Index of Mortality 2; PICU: Pediatric Intensive Care Unit; 25(OH)D: Vitamin D; PTH: Parathyroid hormone; ALP: Alkaline phosphatase; All values median (IQR) except otherwise stated.

deficient compared to that of non-deficient group but not statistically significant (**Table II**).

ARDS was observed more often during the stay in non-vitamin D deficient compared to vitamin D deficient group (42.3 *vs.* 22.6%, *P*=0.03). The two groups did not differ in terms of illness severity score at admission, duration of PICU stay, need for mechanical ventilation, duration of ventilator support, septic shock, liver failure and need for renal replacement therapy (**Table II**).

Fifty-nine percent of children had hypocalcaemia at presentation. Secondary hyperparathyroidism was present in 19.8% of hypocalcemic and 19.5% of vitamin D deficient children. All the children in non-vitamin D deficient group who showed secondary hyper-parathyroidism showed evidence of hypocalcemia. PTH responders in vitamin D deficient groups were found to have higher illness severity score at admission compared to non-responders [12.8 (7.4,20.6) *vs.* 6.5 (2.5,12.2), *P*=0.01]. There was no difference in mortality or other clinical outcomes in PTH responders compared to non-responders during PICU stay (**Table III**).

There was no correlation between admission level vitamin D and calcium (r=0.08, *P*=0.3) or PTH (r=-0.14, *P*=0.06). Negative correlation was observed between illness severity score and admission level total calcium corrected for albumin (r=-0.32, *P*<0.001) and admission level albumin (r= -0.31, *P*<0.001).

DISCUSSION

We documented a high prevalence (83.1%) of vitamin D deficiency in critically ill children at admission; only one-fifth of the vitamin D deficient children showed adequate parathyroid hormone response. Vitamin D deficiency was neither associated with higher illness severity nor with worse clinical outcomes. However, among vitamin D deficient children, those who showed adequate parathyroid hormone response were sicker with no difference in mortality or other clinical outcomes compared to those without adequate parathyroid hormone response.

Earlier studies [2-9] have also documented a high prevalence of vitamin D deficiency in critically ill children. Vitamin D deficiency at initiation of critical illness may be due to pre-existing vitamin D deficiency. We did not find association of vitamin D deficiency with illness severity and other poor clinical outcomes. Some studies have shown that lower level of vitamin D at initiation of care is associated with higher admission day illness severity score [5-8]. However, none of them have showed association with mortality and duration of PICU stay. In our study, ARDS was seen more commonly in children with vitamin D sufficient status which is contrary to observations in adults [21].

Only one-fifth of patients with either hypocalcemia or vitamin D deficiency in our study showed adequate parathyroid response. There are inadequate data regarding status of calcium-PTH-vitamin D axis in critically ill children. Literature review in critical care setting in adults identified that secondary hyperparathyroidism was seen in 30-60 % [22,23]. The causes for blunted PTH response remain unclear. Malnutrition and deficiency of magnesium in our study children might have contributed to poor PTH response. Other reasons could be abnormalities of calcium sensing receptor, abnormalities of vitamin D receptor or impairment of 1 α-hydroxylation in critical care setting. Regardless of percentage of PTH responders, it was seen from our study and some studies in adult that vitamin D deficient patients with adequate PTH response had paradoxically higher illness severity score at admission compared to non-responders. There is no clear explanation for such observation. We hypothesize that pleiotropic actions of vitamin D in critical illness may be related to action of $1,25 (OH)_2D$ at tissue level. $1,25(OH)_2D$ is the metabolically active form which is formed from 25(OH)D by the activating enzyme 1 α-hydroxylase. This conversion is under the endocrine and paracrine regulation of PTH. Rise in PTH leads to conversion of 25(OH) D to $1,25(OH)_2D$ which is the biochemically active form. However, in sicker patients secondary hyperpara-thyroidism may persist because of tissue vitamin D deficiency. Therefore, lack of adequate PTH response may indicate better tissue vitamin D utilization, and therefore may be associated with lower

TABLE II BASELINE CHARACTERISTICS AND CLINICAL OUTCOME OF STUDY POPULATION BY VITAMIN D STATUS

Characteristics	25(OH)D <20 ng/mL (n=128)	25(OH)D ≥20 ng/mL (n=26)	P value
Demographic and Clinical			
Median age, month (IQR)	48 (6.5- 108)	9.5 (6- 32)	0.04
Malnutrition, *n* (%)	81 (63.2)	20 (76.9)	0.18
Male gender, *n* (%)	81 (63.2)	21 (80.7)	0.08
Presence of chronic illness, *n* (%)	71 (55.4)	15 (57.7)	0.8
Admission season, *n* (%)			
Summer	65 (50.7)	18 (69.2)	0.01
Winter	37 (28.9)	5 (19.2)	
Spring	26 (20.3)	3 (11.5)	
Major Diagnostic Category			
ARI, *n* (%)	14.8 (19)	26.9 (7)	0.09
Cardiovascular system, *n* (%)	8.6 (11)	11.5 (3)	
Infection other than respiratory, *n* (%)	17.1 (22)	7.6 (2)	
Neurological disease, *n* (%)	15.6 (20)	15.4 (4)	
Liver disease, *n* (%)	10.9 (14)	3.8 (1)	
Sepsis at admission, *n* (%)	84 (65.6)	16 (66.6)	0.6
PIM2, median (IQR)	7.5 (3.0-14.4)	6.7 (1.8- 17.7)	0.85
Biochemical			
25(OH)D, ng/mL, median (IQR)	9.9 (6.3-13.7)	26.5 (21.6-43.0)	<0.001
PTH, pg/mL, median (IQR)	35.8 (18.1-57.0)	26.2 (14.6-56.4)	0.43
Secondary hyperparathyroidism, *n* (%)	25 (19.5)	6 (23.1)	0.681
Calcium corrected for albumin, mg/dL, median (IQR)	8.1 (7.3-8.8)	8.8 (8.2-9.1)	0.02
Hypocalcemia, *n* (%)	83 (64.8)	8 (30.8)	0.001
Serum phosphate, mg/dL, median (IQR)	3.5 (2.9-4.4)	3.9 (3.4- 5.0)	0.20
Serum albumin, mg/dL, median (IQR)	3.2 (2.4-3.7)	3.3 (2.8-3.8)	0.27
Serum ALP, U/ml, median (IQR)	422 (296-611)	465 (318-587)	0.74
Clinical outcomes			
Mortality, *n* (%)	54 (42.1)	14 (53.8)	0.27
PICU length of Stay, median (IQR)	6.5 (3–14.5)	11 (4 –19)	0.07
Requirement of mechanical ventilation, *n* (%)	87 (67.9)	22 (84.6)	0.08
Days of mechanical ventilation, median (IQR)	7 (3-14)	12.5 (4- 20)	0.12
ARDS, *n* (%)	29 (22.6)	11 (42.3)	0.03
Need for RRT during stay, *n* (%)	27 (21.0)	3 (11.5)	0.26
Liver failure, *n* (%)	20 (15.6)	2 (7.7)	0.29
Septic shock, *n* (%)	51 (39.8)	9 (34.6)	0.61

ARI:Acute Respiratory Infection; PIM2: Pediatrics Index Mortality 2; PTH: Parathyroid hormone; ALP: Alkaline Phosphatase; PICU: Pediatric Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome; RRT: Renal replacement therapy.

severity score. It seems   that vitamin D deficiency in conjunction with hyperparathyroidism may be considered as marker of illness severity and not the predictor of any clinical outcome.

    There are some limitations of the study. This was a single center study with heterogeneous groups; while the sample size is similar to previous studies, it is still small for the subgroup analysis. We did not measure vitamin D level at multiple time points which would have given a better picture of vitamin D status as it has been observed that various interventions during initial resuscitation phase

TABLE III BASELINE CHARACTERISTICS AND CLINICAL OUTCOME OF PATIENTS WITH VITAMIN D DEFICIENCY IN THE PRESENCE OR ABSENCE OF PARATHYROID HORMONE RESPONSE

Characteristics	PTH responder (n=25)	PTH non responder (n=103)	P value
Demographic and clinical			
Age in months, median (IQR)	15 (5- 60)	36 (7-108)	0.16
Male gender, *n* (%)	16 (64)	65 (63.1)	0.93
PIM2, median (IQR)	12.8 (7.4- 20.6)	6.5 (2.5-12.2)	0.01
Biochemical			
25(OH)D, ng/mL, median (IQR)	8 (6-12.9)	10 (6.4-14)	0.49
Calcium corrected for albumin, mg/dL, median (IQR)	7.4 (6.6- 8.8)	8.1 (7.4-8.8)	0.06
Hypocalcemia, *n* (%)	18 (72.0)	73 (56.5)	0.15
Serum Phosphate, mg/dL, median (IQR)	4.2 (2.8-4.9)	3.5 (2.9-4.2)	0.15
Serum albumin, g/dL, median (IQR)	4 (2.8- 3.4)	3 (2.4-3.6)	0.09
ALP, µ/mL, median (IQR)	441 (300-1026)	417 (296-576)	0.22
Clinical outcomes			
Mortality, *n* (%)	13 (52)	41 (39.8)	0.26
PICU Length of stay, median (IQR)	7 (3-11)	6 (3-15)	0.82
Requirement of mechanical ventilation, *n* (%)	20 (80)	67 (65)	0.15
Days of mechanical ventilation, median (IQR)	5 (3-11.5)	7 (3-15)	0.30
ARDS, *n* (%)	9 (36)	20 (19.4)	0.07
Need for RRT during stay, *n* (%)	8 (32)	19 (18.4)	0.13
Liver failure, *n* (%)	3 (12)	17 (16.5)	0.57
Septic shock, *n* (%)	14 (56)	37 (35.9)	0.06

PIM2: Pediatric Index Mortality 2; ALP: Alkaline phsophatase; PICU: Pediatric Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome; RRT: Renal replacement therapy.

may alter vitamin D level. We could not measure $1,25(OH)_2D$ and Vitamin D binding protein. Magnesium levels were also not measured, deficiency of which might have led to impaired PTH response. In conclusion, vitamin D deficiency is common in critically ill children. There seems to be an impairment in calcium-PTH-Vitamin D axis in critical illness. Vitamin D deficiency with secondary parathyroidism may be considered as a marker of illness severity and is not a predictor of clinical outcome.

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WHAT IS ALREADY KNOWN?

• Vitamin D deficiency is common in critical illness.

WHAT THIS STUDY ADDS?

• There is impairment in Calcium-Parathyroid hormone-Vitamin D axis in critically ill children.

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