Vitamin D deficiency in critically ill children

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Context
Vitamin D is needed for the proper function of different organs of the body. A few studies have assessed vitamin D status in critically ill children and reported the prevalence of vitamin D deficiency (VDD) in the range of 30–71%.
Aim
The objectives of this study were to assess the prevalence of VDD in a pediatric ICU (PICU) patients and to determine whether there is any relationship between VDD and illness severity, mortality, or length of PICU stay.
Design and settings
We carried out a cross-sectional study of serum 25(OH)-vitamin D levels, measured during the first day of admission to a 10-bedded medical PICU at the Children's Cairo University.
Materials and methods
We analyzed demographic data, pediatric risk of mortality III, and pediatric logistic organ dysfunction between normal and VDD groups in the PICU.
Results
The prevalence of VDD was 44% and that of severe VDD was 34% in critically ill Egyptian children at the onset of critical illness. The median level of vitamin D in the whole group was 59 nmol/l and in deficient group it was 17 nmol/l. Infants had higher median vitamin D levels than those above 1 year of age, but with no statistical difference. VDD patients had higher pediatric logistic organ dysfunction (12 vs. 10; P=0.001) and lower platelet counts (240 vs. 331; P=0.021). Pediatric risk of mortality III, inotropes, sepsis, ventilation, duration of PICU stay, and mortality were not related to VDD.
Conclusion
VDD is highly prevalent in critically ill children and is observed to be associated with organ dysfunction on admission.

Keywords:
organ dysfunction, pediatric critical illness, vitamin D deficiency

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Introduction

The role of vitamin D in metabolism and homeostasis in the general population is well established, but there is now growing interest in its potential association with acute and critical illness [1]. Acute drops in serum concentrations of vitamin D during critical illness due to increasing tissue demands and impaired compensation by concurrent inflammation and organ dysfunction may prolong critical illness pathophysiology [2]. The question about whether vitamin D deficiency (VDD) is involved in multiple organ dysfunction is not yet answered. Seven studies from different pediatric ICUs (PICUs) around the world have been published thus far, including North America, Atlanta, Canada, Australia, Spain, and two Indian PICUs. All these studies showed a high prevalence of VDD in the range of 30–71%. Only Ponnarmeni *et al.* [3] from north India limited his study to critically ill children with sepsis. This study investigated the hypothesis that VDD might be related to higher severity scores and organ dysfunction. The primary objective of this study was to estimate the prevalence of VDD in a group of critically ill children, and the secondary objectives was to correlate vitamin D status with pediatric logistic organ dysfunction (PELOD) and pediatric risk of mortality III (PRISM III) scores.

Materials and methods

We included 88 children from 1 month to 12 years of age, admitted to a 10-bedded medical PICU at the Children's Cairo University. The Children's Cairo University institutional review board approved the study. After obtaining informed consent, parents were interviewed about the order of the child among his or her siblings, time spent outdoor exposed to the sun, and intake of vitamin D-containing foods and

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supplements during weaning. Parents of infants younger than 1 year provided a breastfeeding or artificial formula history. We recorded height and weight percentiles and calculated BMI. Sepsis grade was determined according to the definitions of the International Pediatric Sepsis Consensus Conference [4]: *sepsis*, Systemic inflammatory response syndrome (SIRS) in the presence or as a result of suspected or proven infection; *severe sepsis*, sepsis plus one of the following: cardiovascular dysfunction, acute respiratory distress syndrome, or two or more organ dysfunctions; and *septic shock*, sepsis and cardiovascular organ dysfunction.

Severity of illness was assessed within the first 24 h of PICU admission with the PRISM III score using 16 variables [5], and organ dysfunction was assessed by the PELOD score including six organ systems (neurologic, cardiovascular, renal, respiratory, hematologic, and hepatic), each with up to three variables (total 12 variables). Each variable was assigned points (0, 1, 10, or 20) on the basis of the level of severity [6]. The maximum level of vasopressor used during PICU stay was calculated by using the Sequential Organ Failure Assessment Cardiovascular (CV-SOFA) score [7]. Venous blood samples for the detection of total serum calcium and phosphorus were analyzed at the same time as for vitamin D, but unfortunately ionized calcium was not available at that time in the hospital laboratory. Vitamin D biological samples were collected within the first 24 h of admission to the PICU. Samples were stored at −80 and analysis performed using enzyme-linked immunosorbent assay developed by Immunodiagnostic, Bensheim and Biomedical (Immunodiagnostik AG, Stubenwald-Allee 8a, D Benshieum, Bergstrabe distriction, Germany). A total of 200 µl of prediluted serum sample and control standard were incubated separately for 1 h at 8–10°C after washing; 100 µl of enzyme conjugate was added into each well and incubated for 1 h at 8–10°C; and after washing, 200 µl of the substrate solution was added into each well and incubated for 30 min at room temperature without shaking (protected from direct sunlight). Finally, 50 µl of stop solution was added to each well, and the absorbance was read at 450 nm. VDD was defined as 25(OH) D concentrations below 50 nmol/l, and severe deficiency was defined as concentrations below 30 nmol/l [8–10].

Descriptive statistics are presented with results for continuous variables, provided as means with SDs or medians with minimum and maximum or interquartile ranges and percentages. Associations between vitamin D, patient characteristics, and outcome variables were measured by Fisher's tests for categorical variables and the Mann–Whitney or the Kruskal–Wallis tests for continuous variables, where appropriate. Survival analysis was performed using the Kaplan–Meier procedure to compare the time to death or discharge in the deficient versus normal level vitamin D group.

Results

Prevalence of vitamin D deficiency in the study

Thirty-nine out of 88 (44%) critical children had VDD (level<50 nmol/l), with median vitamin D levels of 17 nmol/l (95% confidence interval: 12–25) in the VDD group as shown in Table 1, whereas 30/88 (34%) children had serious deficiency (<30 nmol/l) (Table 3).

Demographic variables of the study population

The age range was from 1 month to 12 years with a median of 36 months; 43% were girls and 57% were boys. Respiratory disorders were the most common diagnosis in 45% (43% pneumonia and 2% for status asthmaticus), neurological disorders in 22.7% (coma in 15.9%, Guillain–Barré syndrome 4.5%, status epilepticus 2.3%), heart failure in 10.5%, diabetic ketoacidosis in 6.8%, elective postoperative illness in 4.5%, acute hemolytic crises in 3.4%, inborn errors of metabolism in 2.2%, hepatic encephalopathy in 2.2%, septic shock in 1.1%, aplastic crisis in 1.1%, and diabetic ketoacidosis in 6.8%, as shown in Table 2. Patients with chronic disorders represented 42% of the patients, and the majority of them were admitted to the PICU for acute infections along with their chronic conditions. In all, 86% of the admitted infants were exclusively breast fed, and 35% received vitamin D supplementation before admission. Sepsis was present in 82% of cases, and ventilated patients represented 49% of the admissions. The median duration of stay was 6 days, and the maximum PICU stay was 83 days.

Characteristics of the vitamin D deficiency group

The study sample was categorized according to age: above and below 1 year of age. After analyzing vitamin D levels, the median was observed to be higher in infants below 1 year of age, but with no statistical difference (46 vs. 62) (P=0.138). VDD was more common among children with no vitamin D supplementation (P=0.01) and no

Table 1 Vitamin D level in the study population

	Median (minimum–maximum)	Upper CI	Lower CI
In the whole study group (N=88)	59 nmol/l (0–388)	69 nmol/l	33 nmol/l
In the deficiency group (N=39) (<50 nmol/l)	17 nmol/l	25 nmol/l	12.5 nmol/l

CI, confidence interval.

Table 2 Etiology of the different organ system failure in critically ill children

Diagnostic categories of study population	Respiratory [*n* (%)]	Pneumonia	38 (43.1)
		Status asthmaticus	2 (2.3)
	Neurological [*n* (%)]	Status epilepticus	2 (2.3)
		Guillain–Barré syndrome	4 (4.5)
		Encephalopathy and nontraumatic coma	14 (15.9)
	Cardiovascular [*n* (%)]	Heart failure	9 (10.2)
		Septic shock	1 (1.1)
	Hematological [*n* (%)]	Acute hemolytic crises	3 (3.4)
		Aplastic crises	1 (1.1)
	Metabolic [*n* (%)]	Diabetic ketoacidosis	6 (6.8)
		Inborn error of metabolism	2 (2.2)
		Hepatic encephalopathy	2 (2.2)
	Postoperative [*n* (%)]	Postoperative	4 (4.5)

exposure to the sun ($P<0.001$) before the PICU admission determined by history taking. It was observed that VDD was prominent with increasing number of organ dysfunction but with only a weak correlation with PELOD scores on admission ($P=0.001$, $r=-0.370$) (Fig. 1). Children with cardiomyopathy and chronic hepatitis admitted to the PICU had relatively lower vitamin D levels, but their number was not feasible for statistical comparison. Tables 4 and 5 show the comparisons between VDD and normal vitamin D groups: no relation could be observed between VDD and order among siblings, BMI, ventilation, inotropes use, PRISM III (Fig. 3), calcium, phosphorus, and alkaline phosphatase. VDD patients also had lower platelet counts ($P=0.003$, $r=0.321$) as seen in Fig. 2. The majority of study patients had associated sepsis, but this had no statistical relation to VDD. No relation could be observed between mortality or PRISM III and VDD. The VDD group tended to survive for fewer days in the PICU than those with sufficient levels, but there was no statistical difference between deficient and normal vitamin D groups in the survival analysis (Table 5 and Fig. 4).

Discussion

Nearly half of the studied PICU patients (44%) had vitamin D levels less than 50 nmol/l (deficiency) and 30% had severe deficiency with levels below 30 nmol/l.

Table 3 Demographic and clinical characteristics of the study population

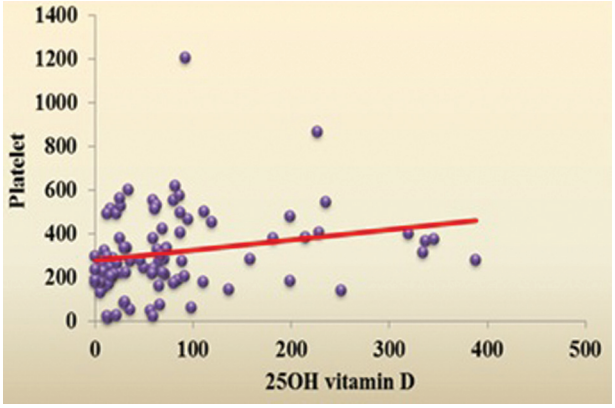
Variables	*N* (%)
Vitamin D levels in the study group (*N*=88)	
>50 nmol/l	49 (56)
<50 nmol/l	39 (44)
<30 nmol	30 (34)
Acute illness in previously healthy children or acute on top of chronic illness in children	
Acute	51 (58)
Acute on top of chronic	37 (42)
Type of milk supplementation	
Artificial	12 (14)
Breast	76 (86)
Vitamin D supplementation before admission	31 (35.2)
Sun exposure	29 (33)
PRISM III score	
Median and IQ	8 (1–24)
CV-SOFA score	
PELOD score	
Median and IQ	12 (0–32)
Diagnosis on admission	
Respiratory failure	40 (45.4)
Neurological failure	20 (22.7)
Cardiovascular failure	10 (11.3)
Metabolic failure	10 (11.2)
Hematologic failure	4 (4.5)
Emergency postoperative	4 (4.5)
Number of organ system failure on admission	
3 or more	50 (56.8)
<3	38 (43.2)
Mechanically ventilated	43 (48.9)
Sepsis	72 (81.8)
Duration of ventilation (days)	
Median (minimum–maximum)	0.0 (0–83)
Duration of stay (days)	
Median (minimum–maximum)	6 (1.0–83)

CV-SOFA, Sequential Organ Failure Assessment Cardiovascular; PELOD, pediatric logistic organ dysfunction.

This high prevalence is similar to other published studies from different PICUs around the world: 40% of PICU patients in North America [11], 60% of PICU patients in Atlanta [12], 34.5% in Australia [13], and 29.5% in Spain [14]. Higher prevalence was observed in other studies, reaching 69% in Canada and 71.4% in India [2,15]. Ponnarmeni *et al.* [3] observed 50% prevalence of VDD among their septic critical children in a north Indian PICU. Dayal *et al.* [16] detected 25% VDD among 92 children admitted to a ward and could detect significant fall in vitamin D levels during hospitalization.

Egypt, similar to other Middle Eastern countries, enjoys a good deal of sunny weather, and therefore it would be expected to have normal levels of vitamin D. However, some of the few studies conducted in Egypt concluded that adult Egyptian females might be

Figure 1



Trend line showing the relation of vitamin D with pediatric logistic organ dysfunction (PELOD) scores.

at higher risk of VDD, and this was not attributed to concealed clothes [17].

Admission diagnoses among the studied children included a variety of medical critical conditions, whereas postoperative patients comprised only 4% with the exclusion of cardiac surgical patients, unlike McNally and Ripple; both had a large category of postoperative cardiac and surgical diagnoses. Madden *et al.* [11] excluded cardiac surgical cases because of the effect of cardiac bypass on vitamin D levels. Rey and colleagues demonstrated a link between vitamin D and respiratory, metabolic, and renal diagnoses. Hebbar and colleagues observed significant VDD in critically ill asthmatic children. In our study, the recorded values of vitamin D showed noticeably

Table 4 Clinical and laboratory data according to vitamin D status

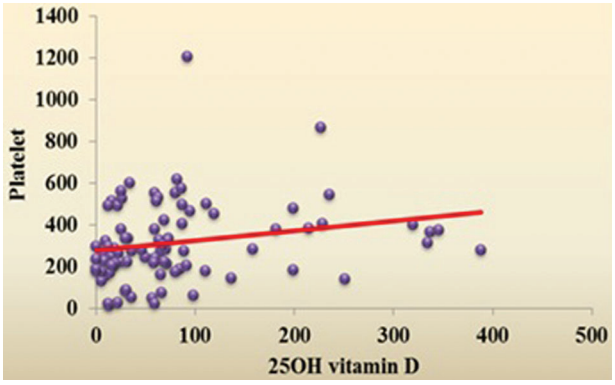
Clinical and laboratory data	Adequate (>50 nmol/l) (*n*=49/88) [*n* (%)]	Deficient (<50 nmol/l) (*n*=39/88) [*n* (%)]	*P* value
Acute illness	28/49 (55)	23/39 (45)	0.86
Acute on top of chronic illness	16/39 (43.2)	21/49 (56.8)	
Order in siblings			
1st	17/49	14/39	0.98
2nd	21/49	17/39	
3rd	9/49	6/39	
4th	2/49	2/39	
Type of milk supplementation			
Artificial	9/49 (75)	3/39 (25)	
Breast	40/49 (52.6)	36/39 (47)	0.147
Good sun exposure	26/49 (74)	4/39 (10.3)	<0.001
Vitamin D supplementation	23/49 (74.2)	8/39 (25.8)	0.01
BMI [median (min–max)]	15 (3.4–20)	15 (8–24)	0.56
Manifestations of rickets	10/49	8/49	0.99
Age<1 year frequency [median (min–max)]	37/88	–62 (7–388)	0.138
Age>1 year frequency [median (min–max)]	51/88	–46 (0.0–344)	
PRISM III score median (min–max)	8 (1–24)	10 (1–19)	0.133
PELOD median (min–max)	10 (0–31)	12 (0–31)	0.001
CV-SOFA	0 (0–4)	0 (0–4)	0.765
Mechanical ventilation %	53.5%	46.5%	0.686
Duration of stay	46 (1–83)	22 (1–56)	0.445
Phosphorus (mg/dl)	4.0 (0.8–7.1)	4.0 (0.7–8.2)	0.58
Calcium (mg/dl)	9.4 (6.611.9)	9.2 (6.7–11.6)	0.41
AST (U/l)	38 (13–2250)	35 (13–2340)	0.9
ALP (U/l)	120 (50–445)	120 (53–501)	0.659
Creatinine (mg/dl)	0.5 (0.1–5.9)	0.6 (0.2–5.0)	0.069
Platelet count ($\times 10^3/mm^3$)	331 (24–1204)	240 (15–602)	0.021
Mortality %	56%	44%	0.97

ALP, alkaline phosphatase; AST, aspartate aminotransferase; CV-SOFA, Sequential Organ Failure Assessment Cardiovascular; PELOD, pediatric logistic organ dysfunction; PRISM III, pediatric risk of mortality III.

Table 5 Kaplan–Meier survival curves according to vitamin D levels

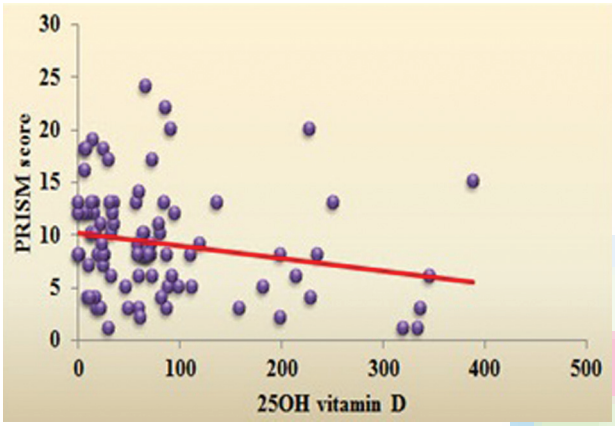
	Number of cases	1st week	2nd week	3rd week	1st month	2nd month	Number of deaths	Median days	*P* value
25 (OH) vitamin D									
>50 nmo/l	49	81	68	68	68	28	14	46	
<50 nmol/	38	85	67	58	34	17	11	22	0.445

Figure 2



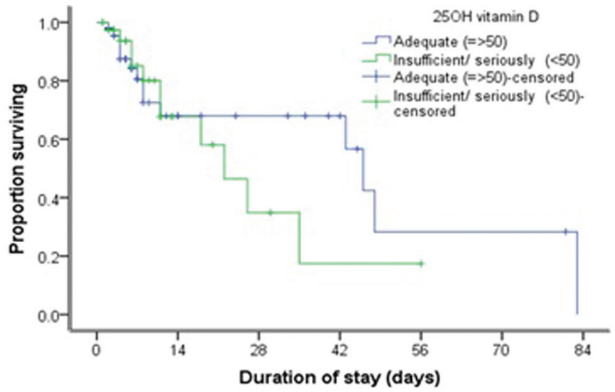
As it demonstrates platelets and vitamin D.

Figure 3



Trend line showing the relation of vitamin D with pediatric risk of mortality III (PRISM III) scores.

Figure 4



Survival analysis according to vitamin D levels.

lower levels among patients with diabetic ketoacidosis, cardiomyopathy, and hepatic failure, but this was just an observation that was not feasible for statistical analysis because of the small sample size of the subgroups. In chronic hepatic patients who presented with fulminant hepatitis, parents provided a history of routine vitamin D supplementation with vitamin D_3. The role of vitamin D in the pathogenesis of diabetes is well known [18], but whether the marked deficiency had a role in diabetic ketoacidosis precipitation or whether this is a sequence of the critical illness still needs to be investigated. One patient with dilated cardiomyopathy had unrecordable vitamin D levels and died. Further research in category-specific critical illness would be helpful to explore the possible relation between VDD and deterioration of chronic illnesses such as cardiomyopathy and chronic hepatic patients.

Children older than 1 year had lower median vitamin D levels in our group, but this difference had no statistical significance. However, published studies have shown controversial results. Although Madden *et al.* [11] and Rey *et al.* [11,14] reported relevance of VDD with age, others found no relation between age and VDD [2,3,13]. Sun exposure and vitamin D supplementation were strongly protective against deficiency. An explanation for this may be that acute stress and critical illness are a state of mismatch between substrate supply and tissue requirement, and those with good reserve may have sufficient stores despite maximal stimulation. Variations in individual patient responses to acute stress and critical illness may therefore depend on baseline vitamin D levels and the extent of tissue requirement [19]. All of the previous pediatric critical care studies, with the exception of the study by Madden *et al.* [11] and Hebbar *et al.* [12], could not document a seasonal difference for VDD.

In our study, only admission PELOD was higher with VDD. Studies from the Boston Children's Hospital and Canada have demonstrated that VDD is associated with only increased illness severity measured by PRISM III and generally reflected longer hospital stays [2,11]. Ayulo *et al.* [20] did not find a significant correlation between PELOD score and vitamin D levels in critically ill children. Reye, Ripple, Lodha, and Ponnarmeni could not find an association between mortality risk prediction, mortality, or hospital stay and vitamin D levels. Dayal could not find any relation between patients who required ventilation and inotropes and with nosocomial sepsis and VDD among 92 patients admitted to the ward. It is noted that the PELOD score is used as an indicator of organ dysfunction unlike the PRISM III, which is validated as a good predictor for mortality.

The high mortality of 28% has many contributing factors such as delayed PICU admission due lack of beds, poor access to appropriate care, high percentage of multiple organ failure, and septic shock. Gemke and

Bonsel [21] in a multicenter study showed a mean 7.1% mortality (range=1–10%) in PICU patients; one of the reasons for this variable mortality was related to the different severity of disorders. El-Nawawy [22] showed 38% PICU mortality, but in India this was 35% [23] and in Argentina it was lower (2.6%) [24].

There was a tendency toward less ICU stay in the VDD group, as the cases were either discharged or died earlier than those with sufficient vitamin D, but this finding was not statistically significant.

Limitation of the study

The present study included small groups of cardiomyopathy, liver failure, and diabetic ketoacidosis patients and could not document the clinical observation of VDD as a contributing factor for their deteriorating medical condition. In addition, the VDD mortality group was observed to survive less in the ICU, but this also was not statistically different. We had no baseline data about vitamin D levels in the general Egyptian pediatric population, and 16% of the patients had vitamin D levels above 150 nmol/l because of the faulty outpatient practice of using repeated large doses of intramuscular cholecalciferol (vitamin D) based on clinical manifestations of rickets without a baseline vitamin D assay.

Conclusion

VDD prevalence was reported in about half of the critically ill patients, and it was observed to be related to multiple organ dysfunctions and rapid clinical deterioration.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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