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The prevalence of vitamin D deficiency and its relationship with disease severity in an urban pediatric critical care unit

Ayulo M Jr, Katyal Ch, Agarwal Ch, Sweberg T, Rastogi D, Markowitz M, Ushay HM

The Children's Hospital at Montefiore, Pediatric Critical Care Medicine, Bronx, NY, USA
E-mail: ckatyal@montefiore.org

Objective. To evaluate the prevalence of vitamin D deficiency among patients admitted to a Pediatric Critical Care Unit (PCCU) in an urban children's hospital, and to assess if there is a correlation between vitamin D level and disease severity.

Patients and Methods. Patients (216) between the ages of 1-21 years admitted to the PCCU in a children's hospital, excluding those readmitted with a previous vitamin D level, were enrolled. Serum 25-OH vitamin D levels were measured in all patients within 24 h of admission to the PCCU. The severity of patient illness was assessed by the Pediatric Logistic Organ Dysfunction (PELOD) score determined on admission.

Results. Vitamin D deficiency was found in 28% of patients and vitamin D insufficiency was found in 47% of patients. Adolescent age group, female gender, Black race, winter season, and increasing BMI were determined to be risk factors associated with vitamin D deficiency. No significant correlation was found between vitamin D level and PELOD score (p=0.09). There were six deaths (3%), 5 (83%) of which occurred in patients with low vitamin D levels. Total serum calcium levels correlated with vitamin D (p=0.005) and PELOD score (p=0.001). However, ionized calcium levels did not significantly correlate with vitamin D (p=0.62) or PELOD score (p=0.26).

Conclusions. Vitamin D deficiency is common in children admitted to an urban inner city PCCU, with 75% of patients having abnormal levels. We did not find a significant correlation between disease severity as measured by PELOD score and vitamin D level in a heterogeneous group of critically ill children. Total serum calcium levels significantly correlated with vitamin D and disease severity in this population. There appears to be an association between vitamin D deficiency and mortality.

Key Words: vitamin D, children, pediatrics, critically ill, PELOD, prevalence, disease severity, hypocalcemia, ICU; mortality

The major circulating form of vitamin D is 25-hydroxyvitamin D [25(OH)-D], and its level is the best available indicator of total vitamin D status (Misra et al. 2008). Although the precise levels that would define the vitamin D adequacy are under debate, several studies have examined the distribution of vitamin D levels in the pediatric population. Using a 25(OH)-D level of ≤ 20 ng/ml as the definition of vitamin D deficiency, Gordon et al. (2004, 2008) have reported that 12.1% and 24% of healthy U.S. infants/toddlers and adolescents, respectively, were deficient. When a cutoff of 15 ng/ml was employed, as was done in the National Health and Nutrition Examination Survey (NHANES), 9% of children were vitamin D deficient, representing 7.6 million US children. Categorizing children with 25(OH)-D levels between 15 and 30 ng/ml as insufficient, an estimated 51 million children would have an insufficient vitamin D status (Kumar et al. 2009).

Corresponding author: Chhavi Katyal, MD, The Children's Hospital at Montefiore, Pediatric Critical Care Medicine, 3415 Bainbridge Avenue, Bronx, NY 10467; phone: (718) 741-2470; fax: (718)654-6692; e-mail: ckatyal@montefiore.org.

In adults, low concentrations of vitamin D have been linked to an increased risk of many diseases including osteoporosis, hypertension, ischemic heart disease, type I diabetes, and cancer (Holick 2007). A cross-sectional study also revealed a relationship between vitamin D levels and lung function, as measured by FEV_1 and FVC (Black and Scragg 2005). Aside from rickets, morbidity associated with vitamin D deficiency among pediatric patients has not been well defined. Recently, low vitamin D levels have been linked with increased markers of allergy and asthma severity (Brehm et al. 2009; Freishtat et al. 2010; Searing et al. 2010). Kumar et al. (2009) demonstrated that vitamin D deficiency in children and adolescents was associated with cardiovascular risk factors, including hypertension and low HDL cholesterol levels.

Vitamin D is a major regulator of calcium metabolism, and its deficiency can result in hypocalcemia. In critically ill pediatric patients, hypocalcemia has been associated with increased mortality (Broner et al. 1990; Cardenas-Rivero et al. 1989; Singhi et al. 2003). A prospective study of vitamin D status in adult ICU patients referred to endocrinologists revealed > 50% were vitamin D deficient, of which only 5% were hypocalcemic (Lee et al. 2009a). Other studies have shown a direct correlation between vitamin D and calcium levels in critically ill adults, suggesting that vitamin D deficiency plays an important role in unexplained hypocalcemia among acutely ill patients (Desai et al. 1987). A case series reported 17 pediatric patients needing admission to intensive care for either dilated cardiomyopathy or respiratory failure secondary to intractable hypocalcemic seizures as a consequence of vitamin D deficiency (Maiya et al. 2006). Two studies have shown a correlation between vitamin D deficiency and critical illness in pediatrics. Mc Nally et al. (2012) have found that lower levels of vitamin D were associated with hypocalcemia, catecholamine utilization, and significant fluid bolus administration. Vitamin D deficiency was independently associated with a longer PICU length of stay and increasing severity of illness as determined by the Pediatric Risk of Mortality score. Madden et al. (2012) have also found that lower levels were associated with a higher admission of daily illness severity.

In this paper, we report the prevalence of vitamin D deficiency among patients admitted to an urban Pediatric Critical Care Unit (PCCU) and discuss the relationship between serum vitamin D level and disease severity.

Patients and Methods

Study population. During the 6-month study period from February 8, 2010 to August 8, 2010, all patients between the ages 1-21 years admitted to the PCCU at the Children's Hospital at Montefiore, were deemed candidates for enrollment. Any patient readmitted to the PCCU with a previously known vitamin D level was excluded. Baseline demographic data, including age, gender, race and ethnicity, height and weight, were collected for all patients enrolled in the study. In addition, diagnosis, severity of illness, and results of laboratory analyses performed within the first 24 h of admission, were also recorded. The Children's Hospital at Montefiore is located in the Bronx, New York. Approximately 90% of the PCCU admissions come from the surrounding urban area, where the percentage of families with incomes below the poverty level is 3 times that of the 9.2% national average (Mc Nally et al. 2012). The severity of patient illness was assessed with the use of the Pediatric Logistic Organ Dysfunction (PELOD) score upon admission to the PCCU (Madden et al. 2012). The Institutional Review Board of Montefiore Medical Center approved the research protocol.

Vitamin D measurement. A 25(OH)-D level was obtained during the first 24 h of admission. The 25(OH)-D level was measured using a DiaSorin 25 OH vitamin D TOTAL assay. The intra- and inter-assay coefficients of variation are 2.9-5.5% and 6.3-12.9% respectively, with a lower limit of detection of 7 ng/ml (U.S. Census Bureau 2011). Patients with 25(OH)-D levels less than 15 ng/ml were classified as deficient, those with levels between 15-29 ng/ml were classified as insufficient, and those with 30 ng/ml and above were classified as sufficient (Kumar et al. 2009).

Statistical analysis. 25(OH)-D levels were categorized into three groups: sufficient (≥ 30 ng/ml), insufficient (15-29 ng/ml) and deficient (< 15 ng/ml). Demographic variables and serum biomarkers were compared among the three groups by ANOVA followed by Bonferroni *post hoc* analysis or its non-parametric counterpart depending on the distribution of the variable. Linear regression models were developed to identify independent factors associated with 25(OH)-D levels. Demographic variables and biomarkers that reached statistical significance ($p<0.05$) on univariate analysis were included in the model. Statistical significance was set *a priori* at 0.05. All analyses were done on STATA version 10 (College Station, TX).

Results

During the 6-month study period from February 8 to August 8, 2010, there were 501 admissions to the PCCU. Of the 501 patients admitted, 119 were less than 1 year of age and excluded from the study. Of the remaining 382 patients, 254 had blood drawn for 25(OH)-D level determination within the first 24 h of admission. Of the 254 blood specimens, 38 were found to be "quantity not sufficient" (QNS), thereby leaving 216 patients with 25(OH)-D levels for study. Patient characteristics and vitamin D levels with subgroup stratification data are shown in Table 1. Patient age was divided into two subgroups; 1 to 11years and 12 to 21 years, in order to distinguish children (1-11 years) from adolescents (12-21 years). Additionally, in order to compare the subgroups by season, spring and winter seasons were combined due to the colder and cloudy nature of spring in the northeastern United States. Of the entire study cohort, 61 patients (28%) were found to have 25(OH)-D levels less than 15 ng/ml consistent with vitamin D deficiency. An additional 102 patients (47% of total) had 25(OH)-D levels between 15 and 29 ng/ml and are classified as vitamin D insufficient. In total, 163 (75%) patients had vitamin D levels that were either deficient or insufficient.

To identify risk factors for vitamin D deficiency, univariated analysis of clinical characteristics of patients who had 25(OH)-D levels less than 15 ng/ml was performed (Table 2). Adolescents aged 12 to 21 years were found to be at a greater risk for vitamin D deficiency than children aged 1-11 years (OR 5.6, 95% CI 2.3-13.6, p<0.001). Across all ages, male patients are at less risk for vitamin D deficiency than females (OR 0.47, 95% CI 0.2-1.0, p=0.049). In comparing the risk of vitamin D deficiency across races and ethnicities of the study population, it was found that persons of the Black race were at greater risk for vitamin D deficiency (OR 2.4, 95% CI 1.1-5.4, p=0.025). In contrast, patients of Hispanic origin showed a tendency towards a decreased

Table 1

Patient characteristics with subgroup stratification

			25(OH)-D Level		
			<15 ng/ml	15-29 ng/ml	≥30 ng/ml
	Characteristic	No. (%)	No. (%)	No. (%)	No. (%)
All		216	61 (28)	102 (47)	53 (25)
Sex					
	Female	118 (55)	40 (34)	53 (45)	25 (21)
	Male	98 (45)	21 (21)	49 (50)	28 (29)
Age					
	1-11 yrs	122 (56)	19 (16)	65 (53)	38 (31)
	12-21 yrs	94 (44)	42 (45)	37 (39)	15 (16)
Ethnicity					
	Hispanic	59 (28)	10 (17)	32 (54)	17 (29)
	Black	82 (39)	32 (39)	33 (40)	17 (21)
	White	24 (12)	4 (17)	16 (66)	4 (17)
	Multiracial	40 (19)	11 (28)	16 (40)	13 (32)
	Asian	3 (1)	2 (67)	0 (0)	1 (33)
Season					
	Summer	78	14 (18)	43 (55)	21 (27)
	Winter/Spring	138	47 (34)	59 (43)	32 (23)
Management					
	Medical	125 (58)	34 (27)	59 (47)	32 (26)
	Post-Operative	91 (42)	27 (30)	43 (47)	21(23)
Outcome					
	Death	6 (3)	4 (66)	1 (17)	1 (17)
	Survivors	210 (97)	57 (27)	101 (48)	52 (25)

risk for vitamin D deficiency (OR 0.42, 95% CI 0.17-1.0, p=0.056). Seasonal differences were also noted in patients admitted in the summer being at a decreased risk for vitamin D deficiency when compared to subjects studied in the winter and spring (OR 0.45, 95% CI 0.2-1.0, p=0.054). Body mass index (BMI) was found to correlate inversely with vitamin D levels (r=-0.2; p=0.005) (Table 3).

A multivariate regression analysis for vitamin D levels was performed and identified increasing age and BMI as independent risk factors for low vitamin D levels. This model was also adjusted for season, race and sex (Table 4).

When evaluating the disease severity, no significant correlation was found between vitamin D levels and PELOD score (r=-0.11; p=0.09). Nor was a significant correlation found between vitamin D level and PELOD score when the subjects with a PELOD score of zero were removed (r=-0.19; p=0.07) (Table 3). A comparison of PELOD score between the deficient group and sufficient group was performed for the entire study cohort and the postoperative and medical subgroups (Table 5). In all groups, the mean PELOD score was higher by gross inspection in the deficient group than the sufficient group. These gross differences were amplified by including only patients with non-zero PELOD scores. Analysis of the data by Wilcoxon two-sample test revealed one significant difference; a PELOD score of 13.1 ± 9.6 for the subgroup of vitamin D deficient medical patients with non-zero PELOD scores compared with a mean PELOD of 5.5 ± 5.9 (p=0.045) for the medical subgroup with sufficient vitamin D levels.

A significant correlation was found between vitamin D level and total serum calcium levels (r=0.19; p=0.005), but this correlation was not seen between vitamin D and ionized calcium levels (r=0.048; p=0.62) (Table 3). A highly significant correlation was found between PELOD score and total serum calcium levels (r=-0.232; p=0.001), but none was found between PELOD score and ionized calcium levels (r=-0.11, p=0.26). Total serum calcium correlated significantly with ionized calcium level (r=0.51, p<0.001).

Table 2

Risk factors for vitamin D deficiency in a PCCU

Characteristic		Odds Ratio	95% CI	p-value
Age				
	1-11yrs	Reference	2.3-13.6	<0.001
	12-21yrs	5.6		
Season				
	Winter/ Spring	Reference	0.2-1.0	0.054
	Summer	0.45		
Sex				
	Female	Reference	0.2-1.0	0.049
	Male	0.47		
Ethnicity				
	Hispanic*	0.42	0.17-1.0	0.056
	Black*	2.4	1.1-5.4	0.02

Univariate analysis of clinical characteristics in 25(OH)-D <15 ng/ml group. Black Race consists of patients of African-American, African and Afro-Caribbean descent. Abbreviations: yrs - years
* When compared to all other ethnicities

Table 3

Correlation of variables with vitamin D level and PELOD score

Variable	r-value 25(OH)-D Level	p-value 25(OH)-D Level	r-value PELOD Score	p-value PELOD Score
BMI	-0.2	0.005	---	---
PELOD Score	-0.11	0.09	---	---
PELOD Score (non-zero scores only)	0.19	0.07	---	---
Total Serum Calcium	0.19	0.005	-0.232	0.001
Ionized Calcium	0.048	0.62	-0.11	0.26

Abbreviations: BMI - body mass index

Discussion

In a heterogeneous group of critically ill children we found a prevalence of vitamin D deficiency that is three times the rate reported in healthy children and adolescents across the United States, 28% vs. 9% (Kumar et al. 2009). Our prevalence of vitamin D deficiency is similar to that reported by Gordon et al. (2004) in examining a similar urban northeastern population, where 24% of healthy adolescents in Boston were vitamin D deficient. The prevalence of vitamin D deficiency in our critically ill adolescent population is even considerably higher at 45%. This is similar to the 47% and 52% reported in two studies of adult ICU patients (Lee et al. 2009a; Leteurtre

Table 4

Independent risk factors for low vitamin D levels in a PCCU

Variable	β	95% CI	*p*-value
Age	-7.05	(-11.9) - (-2.2)	0.005
BMI	-0.31	(-0.6) - (0.03)	0.03

Multivariate regression model for vitamin D levels
Also adjusted for season, race, and sex
Abbreviations: BMI - body mass index

et al. 2003). Pediatric studies have reported a higher percentage (57%) of vitamin D deficiency in adolescents (Madden et al. 2012). On further analysis, we found that adolescent age, female gender, Black race, winter season and high BMI were all factors associated with lower vitamin D levels in our PCCU patients. This coincides with what has been documented previously regarding the factors associated with vitamin D deficiency among healthy children and adolescents (Gordon et al. 2004; Kumar et al. 2009). Of interest, patients of Hispanic race were at decreased risk of vitamin D deficiency. The nature of this protection from vitamin D deficiency is unexplained.

In an attempt to relate disease severity with vitamin D level, we did not find a significant correlation between vitamin D level and PELOD score. Within our cohort, 58% of patients were found to have no organ dysfunction as per PELOD criteria resulting in a score of zero. We evaluated the relationship between vitamin D level and PELOD score in those patients with one or more organ dysfunction as per PELOD criteria. The correlation approached but did not reach statistical significance (r=-0.19; p=0.07). Moreover, in the subgroup of medical patients, there was a significant difference between the mean non-zero PELOD score of the vitamin D deficient group and vitamin D sufficient group. In critically ill adults, Lee et al. (2009a) demonstrated that higher Simplified Acute Physiology Score II (SAPS II) correlated significantly with lower vitamin D levels indicating an increased severity of illness in this vitamin D deficient population. Lucidarme et al. (2010) also identified higher SAPS II to be an independent predictor of vitamin D deficiency, yet found no significant association between Sequential Organ Failure Assessment (SOFA) score and vitamin D level. PELOD and SOFA are scoring systems used to predict outcome by assessing the severity of multiple organ dysfunction syndrome (MODS) in critically ill pediatric and adult patients, respectively (Lucidarme et al. 2010). SAPS II, however, is a severity of illness scoring system used to predict outcome in critically ill adults (Le Gall et al. 1993; Lee et al. 2009b).

Table 5

Comparison of PELOD score between 25(OH)-D <15 ng/ml group and 25(OH)-D ≥30 ng/ml group

		25(OH)-D Level		
		<15 ng/ml	≥30 ng/ml	
Characteristic		Mean (Std. Dev.)	Mean (Std. Dev.)	p-value*
All				
	PELOD Score	4.1 (7.3)	2.2 (4.8)	0.123
	PELOD Score (non-zero scores only)	9.0 (8.5)	5.2 (6.3)	0.362
Post Operative				
	PELOD Score	2.6 (4.2)	1.8 (4.9)	0.266
	PELOD Score (non-zero scores only)	5.0 (4.7)	4.6 (7.3)	0.327
Medical				
	PELOD Score	5.4 (8.9)	2.6 (4.8)	0.767
	PELOD Score (non-zero scores only)	13.1 (9.6)	5.5 (5.9)	0.045

Abbreviations: Std. Dev. - standard deviation
**p*-value compares 25(OH)-D <15ng/ml group with 25(OH)-D ≥30 ng/ml group

Studies of Vitamin D levels in critically ill children have used PRISM III scores for measuring severity of critical illness (Madden et al. 2012; U.S. Census Bureau 2011). PRISM III requires data from an arterial blood gas for calculation. We included all patients admitted to the critical care unit, including patients whose condition did not warrant ABG measurement. This inclusion likely diluted our cohort with less severely ill patients. Interestingly, in the subgroup of medical patient's, when patients with 0 PELOD scores were removed from the analysis a significant difference in PELOD scores was found between vitamin D insufficient and sufficient patients.

Despite the lack of correlation with disease severity, the prevalence of vitamin D deficiency (28%) among our patients is substantially higher than the 9% found among the general pediatric population (Kumar et al. 2009). Hypothetical models demonstrating how vitamin D deficiency may be an unrecognized contributor to adverse outcome in intensive care patients have been proposed. Lee et al. (2009b) hypothesized that vitamin D deficient/insufficient states may worsen existing organ dysfunctions in critically ill patients, leading to worse outcomes. Perhaps the effects of low vitamin D levels on disease severity during critical illness are not as straightforward, only affecting the most severely ill patients.

Accumulating evidence suggests that vitamin D deficiency is linked to excess mortality in the general adult population (Lind et al. 2000; Zitterman et al. 2009). Braun and colleagues (2011) demonstrated that vitamin D deficiency before hospital admission is a significant predictor of short and long term all-cause mortality in critically ill adults, despite having 57% of their patients having zero organs with failure. Within our study group, there were six deaths (3%), of which 5 (83%) had low vitamin D levels. These results indicate a need for further investigations into the relationship between vitamin D deficiency and mortality in the PCCU.

In the critically ill adult population, studies have shown a direct correlation between ionized calcium and vitamin D levels (Lacroix and Cotting 2005; Desai et al. 1987; Lee et al. 2009a), whereas others have found a direct correlation between total serum calcium and vitamin D levels (Leteurtre et al. 2003). This relationship has not been evaluated in critically ill children. We found a significant correlation between vitamin D and total serum calcium levels, but no significant correlation was demonstrated between vitamin D and ionized calcium levels. Studies in this population have not found a significant correlation between total serum and ionized calcium levels during pediatric intensive care hospitalization. Ionized calcium is the physiologically active fraction and its level is influenced by protein binding, pH, and free fatty acids. Critically ill patients often have abnormalities in serum protein levels, acid-base status and nutritional state that may alter the relationship of total serum and ionized calcium (Singhi et al. 2003). We did find, however, a significant correlation between total serum and ionized calcium levels on admission in our patients. This may be a reflection of the short duration of critical illness and thus only a mild dissociation between ionized and total calcium.

Hypocalcemia has been associated with increased mortality in critically ill children (Cardenas-Rivero et al. 1989; Broner et al. 1990; Singhi et al. 2003). We evaluated for any correlation between calcium and disease severity. A significant correlation was found between PELOD score and total serum calcium levels, but no correlation was found between PELOD score and ionized calcium levels. Egi and colleagues (2011) conducted a large retrospective multicenter study evaluating ionized calcium concentration and outcome in critical illness. They demonstrated that ionized calcium concentration on admission was not significantly associated with mortality. Abnormalities of ionized calcium occur because of multiple factors and might only be a marker of acute illness rather than a contributor to morbidity (Egi et al. 2011).

Our study has several important limitations. The prevalence of vitamin D deficiency among healthy children and adolescents in the Bronx, New York has not been documented. Another limitation is the use of PELOD score on admission as the only measure of disease severity since we found that most children had scores of zero. Other measures may be better indicators of disease severity such as length of stay, daily PELOD scores, or a pediatric scoring system that measures severity of illness and not severity of MODS.

In summary, vitamin D deficiency is common in children admitted to the PCCU, with 75% of patients in our PCCU having abnormal levels. The adolescent age group, female gender, black race, winter season, and increasing BMI were all risk factors associated with vitamin D deficiency in this group. We did not find a significant correlation between disease severity and vitamin D level in a heterogeneous group of critically ill children. Total serum calcium levels significantly correlated with vitamin D and disease severity among this population. An intriguing association between vitamin D deficiency and mortality as an outcome requires further investigation.

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