The Association of Vitamin D Status With Pediatric Critical Illness

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KEY WORDS
vitamin D, pediatrics, risk factors, length of stay, critically ill children

ABBREVIATIONS
25(OH)D—25-hydroxyvitamin D
AIP—Adrenal Insufficiency in Pediatric Critical Illness Study
ALRI—acute lower respiratory infection
CI—confidence interval
IQR—interquartile range
OR—odds ratio
PRISM—Pediatric Risk of Mortality III

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WHAT’S KNOWN ON THIS SUBJECT: Vitamin D is a pleiotropic hormone important for proper functioning of multiple organs. Adult critical care studies have suggested vitamin D as a modifiable risk factor. No studies have investigated the prevalence, risk factors, or role in pediatric critical illness.

WHAT THIS STUDY ADDS: This study provides evidence that the majority of critically ill children have vitamin D deficiency at the time of PICU admission, and that lower levels are associated with hypocalcemia, catecholamine administration, significant fluid bolus requirements, and longer PICU admissions.

abstract

OBJECTIVES: Vitamin D is a pleiotropic hormone important for the proper functioning of multiple organ systems. It has been hypothesized that vitamin D deficiency could contribute to or worsen outcomes in critical illness. The study objective was to determine the prevalence of vitamin D deficiency, risk factors for its presence, and potential association with clinically relevant outcomes in critically ill children.

METHODS: A prospective cohort study, conducted from 2005 to 2008 in 6 tertiary-care PICUs in Canada. Data and biological samples from 326 critically ill children up to 17 years of age were available for analysis. Total serum 25 hydroxyvitamin D or 25(OH)D was measured by using liquid chromatography-mass spectrometry.

RESULTS: The prevalence of 25(OH)D <50 nmol/L was 69% (95% confidence interval, 64–74), and 23% (95% confidence interval, 19–28) for 25(OH)D between 50 to 75 nmol/L. Lower levels were associated with hypocalcemia, catecholamine utilization, and significant fluid bolus administration. Vitamin D deficiency was independently associated with a longer PICU length of stay (+1.92 days, \( P = .03 \)) and increasing severity of illness as determined by the Pediatric Risk of Mortality score with every additional point increasing the likelihood of being vitamin D deficient by 8% (\( P = .005 \)).

CONCLUSIONS: This study provides evidence that vitamin D deficiency is both common among critically ill children and associated with greater severity of critical illness. Further research will determine whether targeted vitamin D supplementation or rapid restoration will improve outcome. *Pediatrics* 2012;130:1–8
Vitamin D, a nutrient derived from both diet and sunlight, has been increasingly recognized as pivotal to good health. A pleiotropic hormone, vitamin D has been increasingly implicated in the proper functioning of multiple organs, with deficiency states associated with cardiovascular disease, asthma, multiple sclerosis, diabetes, acute lower respiratory infection (ALRI), and cancer.6–9 It was recently hypothesized that vitamin D deficiency could also contribute to or prolong critical care pathophysiology.7,10 A number of adult-based critical care studies support this idea, reporting high deficiency rates in critically ill children.6–9 It was recently hypothesized that vitamin D deficiency would be common in critically ill children.

**METHODS**

This study was a secondary analysis of data and biological samples collected as part of the Adrenal Insufficiency in Pediatric Critical Illness Study (AIP), a prospective cohort study conducted in 7 tertiary-care PICUs (latitude range: 43°N to 53°N) in Canada.15 Briefly, patients were eligible if they were newborn to 17 years of age, had arterial or central venous catheters, and could be enrolled within 24 hours of admission. AIP excluded premature infants; patients with known or suspected adrenal, pituitary or hypothalamic disease; those who received systemic steroids for >10 days in the previous month or more than 1 dose of systemic steroids within 24 hours of admission (except dexamethasone); those expected to have care withdrawn; those transferred from another ICU; or those whose primary physician refused. From June 2005 to July 2008, 4090 patients were admitted to the participating PICUs. Of these, 1707 (42%) met eligibility criteria, and 434 of 2383 patients (18%) were excluded for steroid criteria. The AIP authors compared eligible patients who could not be consented with the final participants, and no significant difference in the Pediatric Risk of Mortality Score III (PRISM) scores (6 [interquartile range: IQR 3 to 10] vs 6 [IQR 3 to 9]; P = .81) or age (P = .72) was evident. Research ethics board approval for the vitamin D substudy was obtained from 6 centers, representing 337 of the original 389 study participants. In AIP, blood samples were collected within 24 hours of admission, and again on day 2. Of the potential 337 substudy participants, day 1 and 2 serum was used for 321 and 5 patients, respectively. Supplemental Fig 2 provides a patient flow diagram.

Total serum 25(OH)D, the metabolic precursor to calcitriol, is considered the best indicator of body stores and vitamin D axis activity. The Ontario Newborn Screening Laboratory calculated total 25(OH)D from samples by using a published liquid chromatography-mass spectrometry procedure measuring both 25(OH)D2 and 25(OH)D3.16 Vitamin D deficiency and insufficiency were defined as 25(OH)D concentrations <50 nmol/L and between 50 and 75 nmol/L.8,9,17,18

Demographic, clinical, and laboratory data were available in a computerized database. Variables used as measures of illness severity, organ dysfunction, and clinical course included PRISM, catecholamine administration, fluid bolus requirements, mechanical ventilation duration, PICU length of stay, and mortality.15,19 Both albumin and lowest pH-corrected ionized calcium levels during admission were obtained from the principal investigators center. Hypocalcaemia was defined as an ionized value <1.1 mmol/L.20,21 Examples of conditions used to classify participants with preexisting illness included developmental delay, seizure disorder, cerebral palsy, genetic condition, congenital heart disease, chronic obstructive or restrictive lung disease, oncological condition, or diabetes. Hepatic dysfunction was defined by using the pediatric logistic organ dysfunction score (PELOD) criteria, including aspartate aminotransferase >950 and international normalized ratio >1.4.22 Malnutrition was assessed by using the Gomez approach or weight for age ratio.23 Classification of noncardiac surgical categories is shown in Supplemental Table 6. The prevalence of vitamin D deficiency and insufficiency were calculated with 95% confidence intervals (CI). Descriptive statistics were presented with results for continuous variables provided as either means with standard deviations or medians with IQRs and

In Canada each year, 10 000 children are admitted to PICUs, resulting in ~40 000 patient days. The identification of previously unrecognized modifiable risk factors could help guide new preventative or therapeutic strategies for pediatric critical illness. Vitamin D supplementation may represent a novel strategy to modulate pediatric critical illness occurrence, intensity, duration, and associated chronic morbidities. Although poor nutritional status is recognized as a risk factor for adverse outcomes in critical illness, there are no published studies investigating the potential role of vitamin D deficiency in pediatric critical illness.1
percentages with 95% CI for categorical variables. Associations between vitamin D, patient characteristics and outcome variables were sought by using χ² and Fisher’s tests for categorical variables, and t tests, Wilcoxon rank sum, Mann-Whitney, or Kruskal-Wallis tests for continuous variables, where appropriate. Multivariate logistic regression was used to investigate the relationship between vitamin D deficiency and patient characteristics. To determine whether vitamin D was independently associated with PICU length of stay, characteristics with a P value <.25 in univariate analysis were considered through multivariate linear regression. A P value <.05 was considered statistically significant. SAS software (version 9.2, SAS Institute, Cary, NC) was used for the analysis.

RESULTS

Demographics

Three hundred eighty-nine critically ill children were enrolled in the AIP study. For the substudy, 25(OH)D measurements were performed on 326 study participants because permission was declined from 1 of the original centers (n = 52), and biological sample was unavailable for 11 participants. Baseline characteristics of the participants are presented in Table 1. The overall cohort had a median age of 3.7 years (IQR: 0.6–13), 51% were boys, and median admission PRISM score was 6 (IQR: 3–10). Two hundred and thirty-five patients (72%) were mechanically ventilated, eighty-eight (27%) received catecholamines, and the median PICU admission length was 4 days (IQR 3–7). A comparison of patient characteristics between vitamin D substudy participants and the 63 excluded AIP participants did not demonstrate statistically significant differences in age, gender, weight, weight for age ratio, season, or PRISM score (Supplemental Table 5). Excluded participants were more likely to have a preexisting illness and be admitted after congenital heart disease surgery.

Risk Factors

Mean total 25(OH)D (D₂ + D₃) was 43.2 nmol/L (SD 19.4). Mean 25(OH)D₂ was 3.2 nmol/L (SD 1.6), and the mean 25(OH)D₃ was 40.2 (SD 19.5). Comparison of 25(OH)D levels for the subjects (n = 174) with available day 1 and day 2 serum did not identify clinical or statistical differences (42.3 ± 19.6 vs 44.1 ± 19.6, P = .10) in 25(OH)D concentrations over time. The prevalence of vitamin D deficiency [25(OH)D₂ plus 25(OH)D₃ <50 nmol/L] was 69% (95% CI: 64–74); with an additional 23% (95% CI: 19–28) having a concentration between 50 and 75 nmol/L. No baseline or admission patient characteristic was associated with vitamin D deficiency in bivariate analysis (P < .05; Table 2). Additional evaluation using a multivariate logistic model only identified weight ratio, trauma diagnosis, and PRISM score as statistically associated with vitamin D deficiency (Supplemental Table 7). Each additional PRISM unit increased the odds of being vitamin D deficient by 8% (odds ratio [OR] 1.08, 95% CI: 1.02–1.14; P = .005). Trauma diagnosis decreased odds of vitamin D deficiency (OR 0.37, 95% CI: 0.14–0.93; P = .034), and higher weight for age ratios (OR 1.14, 95% CI: 1.05–1.28; P = .013) increased odds of vitamin D deficiency. Established risk factors (age and season) and hepatic dysfunction were not independently associated with vitamin D deficiency in the multivariate logistic model.

Illness Severity

Statistically significant differences in 25(OH)D levels were observed between groups with and without specific organ dysfunction and known biochemical markers of illness severity (Fig 1). First, lower mean 25(OH)D levels were observed in the PICU subgroups requiring catecholamine infusion (45 ± 19 nmol/L vs 38.5 ± 16 nmol/L, P = .006) and >40 mL/kg fluid bolus on the day of admission (44.7 ± 19.6 nmol/L vs 34.5 ± 18.5 nmol/L, P = .001). Mechanically ventilated subjects had lower 25(OH)D levels compared with the group not requiring intubation (47.2 ± 19.9 nmol/L vs 41.7 ± 19.1 nmol/L, P = .02). Substudy subjects with at least 1 hypocalcemic episode had significantly lower 25(OH)D levels compared with those with normal or minimally reduced calcium levels (51.0 ± 20.6 nmol/L vs 36.6 ± 15.9 nmol/L, P = .001). Of note, no significant relationship between 25(OH)D levels and serum albumin could be demonstrated (Spearman correlation coefficient –0.08, P = .48). A moderate correlation between albumin and preexisting illness was evident (0.57, P < .001).

Biochemical abnormalities and clinically important outcome measures were compared for study subjects with and without vitamin D deficiency (Table 3). A higher percentage meeting criteria for significant hypocalcemia (78% vs 41%, P = .001) was observed for vitamin D deficient subjects. Lower pH
corrected ionized calcium levels (1.04 vs 1.09 nmol/L) were calculated for the vitamin D deficient group, with the result barely achieving statistical significance (P = .05). Vitamin D deficient participants were more likely to receive catecholamine infusion (30% vs 20%; P = .05); with a highly significant difference observed for those receiving multiple catecholamines (7% vs 0%, P = .007). Finally, a statistically significant difference in median day 1 fluid bolus administration was observed, and twice as many vitamin D deficient study participants required >40 cc/kg fluid bolus on the day of PICU admission (17% vs 8%, P = .04).

**Clinically Important Outcomes**

In multivariate regression, a 25(OH)D concentration under 50 nmol/L was independently associated with an additional 1.92 days of PICU length of stay (range 1.75–1.9 additional days); vitamin D deficiency remained statistically significant in all 3 models (P < .05). Given the PICU mortality rate of 1.5% (5/326), the study was not powered to evaluate for an association with vitamin D deficiency; all 5 deceased patients were vitamin D deficient.

**DISCUSSION**

Data from this multicenter prospective observational study strongly suggests that the majority of critically ill Canadian children are vitamin D deficient at PICU admission. Furthermore, lower 25(OH)D levels are associated with greater catecholamine requirements, fluid bolus administration, hypocalcemia, and longer PICU admission. The mean serum 25(OH)D level of 40 nmol/L measured immediately after admission for 326 critically ill Canadian children demonstrates that many have concentrations well below the target suggested by the Institute of Medicine, Canadian Academy of Pediatrics,17,18,24 American Academy of Pediatrics, and American Academy of Pediatrics.17,18,24 Utilizing 50 nmol/L as the cutoff, 69% of the study cohort was vitamin D deficient. These levels are considerably lower than those reported on healthy Canadian children, with means closer to 75 nmol/L.25–27 Serum 25(OH)D levels on critically ill children appear similar to results from adult ICU studies reporting values ranging from 32 to 61 nmol/L.11–13,28 Levels and deficiency rates are also comparable to those from the 1 identified pediatric study in this area, reporting an average 25(OH)D level of 49 nmol/L in 16 children with severe ALRI requiring PICU admission.14

This study evaluated preadmission characteristics associated with vitamin D status. Contrasting with studies on healthier children no association with age or season was observed in the PICU
Patients with poor nutrition or chronic illness are potentially at higher risk for both greater illness severity and vitamin deficiency. For example, preexisting illness could lead to reduced vitamin D status through abnormal diets, altered metabolism, or reduced environmental ultraviolet exposure. Despite this potential, no association between vitamin D deficiency and either preexisting illness or lower weight for age was demonstrable. In fact, higher weight for age ratios were associated with lower 25(OH)D, findings consistent with existing obesity literature. Furthermore, by using albumin as a marker of poor nutrition, no relationship with 25(OH)D concentration was evident.Trauma was the only other baseline characteristic statistically linked to vitamin D, consistent with the recent publication by Cecchi and colleagues identifying higher 25(OH)D concentrations in critically ill trauma patients relative to a sepsis cohort.

It is likely that the measured 25(OH)D concentrations do not accurately represent the preillness state because both disease and associated interventions could reduce serum levels. Acute, sometimes transient, reductions in vitamin and mineral concentrations have been previously reported after significant hemorrhage, transudative fluid loss, fluid replacement or loading, and renal replacement therapies. Serum 25(OH)D levels may be similarly
TABLE 4 Multivariate Model Demonstrating Variables Associated With PICU Length of Stay

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Univariate Adjustment to PICU LOS (d) (95% CI)</th>
<th>Multivariate Adjustment to PICU LOS (d) (95% CI)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiencyb</td>
<td>1.72 (−0.09 to 3.53)</td>
<td>1.92 (0.17–3.68)</td>
<td>.03</td>
</tr>
<tr>
<td>Medicalc</td>
<td>4.58 (2.52–6.66)</td>
<td>3.45 (1.31–5.59)</td>
<td>.002</td>
</tr>
<tr>
<td>Cardiac Surgery</td>
<td>1.79 (−0.17 to 3.74)</td>
<td>1.16 (−0.96 to 3.28)</td>
<td>.28</td>
</tr>
<tr>
<td>Site D</td>
<td>4.61 (2.56–6.66)</td>
<td>3.84 (1.78–5.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Site C</td>
<td>0.91 (−1.63 to 3.45)</td>
<td>0.77 (−1.87 to 3.40)</td>
<td>.57</td>
</tr>
<tr>
<td>Site D</td>
<td>3.16 (−0.42 to 6.74)</td>
<td>1.29 (−2.43 to 5.0)</td>
<td>.50</td>
</tr>
<tr>
<td>Site E</td>
<td>1.61 (−1.08 to 4.50)</td>
<td>0.86 (−1.80 to 3.53)</td>
<td>.52</td>
</tr>
<tr>
<td>Site F</td>
<td>0.80 (−4.95 to 6.56)</td>
<td>1.66 (−3.97 to 7.29)</td>
<td>.56</td>
</tr>
<tr>
<td>PRISM scorec</td>
<td>0.27 (0.12 to 0.42)</td>
<td>0.15 (0.008 to 0.31)</td>
<td>.06</td>
</tr>
</tbody>
</table>

Cl, confidence limit; LOS, length of stay.
*a* P value is for multivariate analysis.
*b* Vitamin D deficiency defined as a 25(OH)D level <50 nmol/L.
*c* Noncardiac surgical study participants represented the reference group.
*d* Site A was used as the reference, and with the exception of Site B, none of the remaining 4 sites were statistically associated with an adjustment to PICU length of stay.
*e* Each additional PRISM score of 1 unit was associated with an additional 0.15 PICU days, but the finding did not achieve statistical significance.

Reduced in critically ill patients in the acute setting because of altered metabolism, transcapillary leak, and fluid administration.36,37 For example, Krishnan et al recently demonstrated that cardiopulmonary bypass fluid loading transiently reduces serum 25(OH)D by up to 40%.38 Furthermore, Reid et al reported an acute postoperative drop in serum 25(OH)D that only partially recovered.39 Regardless of etiology, the high prevalence of vitamin D deficiency in the early stages of critical illness may be relevant. In fact, acute drops in serum concentrations may be more physiologically relevant than chronic deficiency because time is required for adjustment to lower concentrations, and the extent and time to compensation would be impaired by concurrent inflammation and organ dysfunction.

It has been previously hypothesized that inadequate vitamin D status might predispose to or worsen critical illness pathophysiology. A recent large study by Braun and colleagues evaluating predmission 25(OH)D identified lower concentrations as an independent predictor of ICU survival.14 Numerous other small studies with adult participants have demonstrated relationships between vitamin D deficiency and both the Simplified Acute Physiology score and ICU length of stay.11–13 This study on critically ill children supports these reports, with higher admission illness severity scores (PRISM) being associated with vitamin D deficiency. Similarly, after controlling for admission illness severity and other independent predictors, a 25(OH)D level <50 nmol/L was associated with an almost 2-day-longer PICU stay.

In our cohort, lower vitamin D levels were observed in participants with hypocalcemia, significant fluid bolus requirements, and subgroups requiring cardiovascular and ventilatory support. These findings are consistent with basic science and clinical studies in non-ICU settings revealing vitamin D as a pleiotropic hormone important for proper functioning of organs central to critical illness pathophysiology. First, vitamin D plays a well-established role in calcium homeostasis. Consistent with adult studies, the current study links lower vitamin D status to critical illness hypocalcemia.40,41 Second, vitamin D has been shown to influence cardiac myocyte and endothelial function through cellular receptors, altering gene and protein expression, signal transduction, and enzymatic reactions.42,43 Clinical evidence for a role in cardiovascular health is available from both large adult studies and pediatric case series identifying vitamin D deficiency as a reversible cause of cardiovascular disease and heart failure.44–47

Third, vitamin D receptors are present on major immune blood cell types, modulating white cell proliferation, maturation, cytokine release, antimicrobial peptide, and toll-like receptor levels.48–52 Clinical research has demonstrated associations between vitamin D and severe ALRI, sepsis, and asthma exacerbations.3,7,28 Finally, vitamin D deficiency could impair gas exchange through mechanisms including infection, inflammation, nerve dysfunction, and muscle weakness.53,54 The multifactorial mechanism for vitamin D deficiency in critical illness may also be supported by our finding that the addition of mediators including catecholamines, mechanical ventilation, or significant fluid bolus requirements into the length of stay regression multivariate model each attenuated the strength of association (5% to 15%) with vitamin D deficiency.

This study has a number of strengths. It is the largest study, adult or pediatric, reporting 25(OH)D levels in critically ill patients. Distinct from the majority of the adult ICU studies, 25(OH)D measurements were performed by using uniform methods on blood collected within 24 hours of ICU admission. Additional aspects of the study reduced potential bias, including defined eligibility criteria, and the multicenter multyear enrollment design. A potential limitation of this study is that the original AIP was not intended to estimate the prevalence of vitamin D deficiency or designed to confer causality. Furthermore, the AIP eligibility criteria may limit generalization of study findings to all PICU admissions because only those children ill enough to require central venous or arterial lines were enrolled. However, these children
probably represent the population of interest because they are the ones in whom supplementation may be more important. Finally, blood 25(OH)D may not accurately reflect vitamin D status in ICU patients dysfunction of the parathyroid, and renal organs may limit or prevent conversion of 25(OH)D to calcitriol, active vitamin D(3). A more involved study evaluating all components of the vitamin D axis may demonstrate a stronger relationship with clinically relevant outcomes. In conclusion, this study provides evidence that critically ill children commonly have 25(OH)D concentrations <50 nmol/L, and that lower levels are associated with hypocalcemia, catecholamine need, significant fluid bolus administration, and longer length of stay. Subsequent prospective interventional trials are required to establish whether rapid restoration of vitamin D body stores has an impact on critical illness disease course and outcome.

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