Vitamin D Deficiency and Adrenal Function in Critically Ill Children

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Background: *Data on interrelationship between vitamin D deficiency (VDD) and adrenal insufficiency in critically ill children are limited.*
Objective: *To determine vitamin D status in critically ill children and its relationship with adrenal function.*
Material and Method: *Thirty-two patients and 36 controls were included. Serum 25-hydroxyvitamin D (25-OHD) levels were measured. Pediatric Risk of Mortality (PRISM) III score, outcome and adrenal function assessed by 1-microgram adrenocorticotropic hormone test were collected.*
Results: *Median (IQR) serum 25-OHD of the patients was less than that of the controls (16.6 (13.3-19.5) vs. 24.2 (21.0-27.9) ng/mL, p<0.001). Twenty-five (78%) patients and seven (19%) controls had VDD. PRISM III score, proportions of patients with shock and vasopressive drug used, length of intensive care unit stay and ventilator used, and adrenal function were not different between patients with and without VDD. Patients with serum 25-OHD of less than 12 ng/mL had higher median (IQR) PRISM III score (14 (6-20) vs. 5 (2-10), p = 0.033) and higher proportion of mortality than those with serum 25-OHD of 12 ng/mL or greater.*
Conclusion: *A greater proportion of VDD in critically ill children as compared with that of the controls was demonstrated. Serum 25-OHD was not associated with adrenal function.*

Keywords: *Vitamin D deficiency, Critical illness, 25-hydroxyvitamin D, Adrenal insufficiency, Cortisol*

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Vitamin D deficiency has been reported to be associated with a wide range of conditions in general populations, including infection, metabolic diseases, cancers, and mortality[1,2]. Recently, there have been numbers of interest in the vitamin D status in critically ill patients. Many adult and a few pediatric studies involving critical illness have been reported the association of vitamin D deficiency with increased severity of illness, mortality, length of stay in intensive care unit (ICU), and risk of infection[3-7]. High incidence (30-97%) of vitamin D deficiency has been reported among both critically ill children and adults[5,7-11].

Adrenal insufficiency has frequently been reported in critically ill patients. Similar to vitamin D deficiency, adrenal insufficiency has also been demonstrated to be a detrimental factor associated with poor outcome in critically ill patients. Increased requirement of fluid resuscitation, and increased uses of vasopressor and mechanical ventilation were reported in critically ill patients with adrenal insufficiency[12,13]. As both adrenal insufficiency and vitamin D deficiency were frequent in patients with critical illness and they were associated with unfavorable outcome, therefore, the association between these two conditions may exist. There was a recent study that demonstrated a stronger association between adrenal insufficiency and catecholamine use in the presence of vitamin D deficiency, despite having no association between vitamin D status and adrenal insufficiency[14]. In addition, vitamin D may modulate glucocorticoid effects on cardiovascular system[15]. Despite these findings, the data on interrelationship between vitamin D deficiency and adrenal insufficiency are still limited and not clearly defined.

The present study aimed to assess vitamin D status and the frequency of vitamin D deficiency in critically ill children, and to determine the relationship between vitamin D deficiency and adrenal function as well as the severity of illness in these patients.

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Material and Method

The present study was a secondary analysis of data and blood samples collected as part of the authors' previously published study in adrenal function of critically ill children[16]. Briefly, it was a prospective cohort study undertaken between March 2007 and February 2008 at Ramathibodi Hospital, a tertiary teaching hospital, in Bangkok (13°N latitude). Thirty-two critically ill children, defined as children who needed the ICU admission, were included. They were excluded if they had a history of known adrenal insufficiency, severe liver disease or had received medications known to affect adrenal function. Another 36 healthy children were enrolled during the same period of time and served as the control group. Children in the control group were all healthy, and they all had normal weight, height, and nutritional status. They did not receive supplements or medications at the time of the study. Duration of sunlight exposure was collected.

Data collection and outcomes

Demographic data, severity of illness assessed by Pediatric Risk of Mortality (PRISM) III score[17] and outcome of all patients were collected. The mortality of patients was assessed at the time of hospital discharge. A 1-microgram (mcg) adrenocorticotropic hormone (ACTH) stimulation test for assessing adrenal function was performed within 24 hours of each patient's admission. The control children also underwent the 1-mcg ACTH stimulation test.

Serum samples of patients and controls collected before performing the ACTH stimulation test, which were kept at -80°C, were analyzed for total 25-OHD concentration, which was an indicator of body vitamin D status. Serum levels of total calcium, creatinine, albumin, C-reactive protein and cortisol binding globulin as well as hemoglobin were collected in the patient group.

Serum cortisol was assayed using an immunochemiluminescence method. The serum total 25-OHD level was measured using liquid chromatography-mass spectrometry (LC-MS) method. Vitamin D deficiency and insufficiency were defined as serum 25-OHD levels of less than 20 and between 20-30 ng/mL, respectively[1]. Owing to the recommendation of the Institute of Medicine, serum 25-OHD cut-off level of 12 ng/mL is the lower threshold for adequate vitamin D requirement and below this level is associated with risk of deficiency symptoms[18]. Therefore, the authors chose the serum 25-OHD level of 12 ng/mL for the additional analysis. Adrenal insufficiency was defined as a random serum cortisol level at ICU admission of less than 15.1 mcg/dL, which was the 5th percentile of peak serum cortisol after 1-mcg ACTH stimulation test achieved by the healthy children[16]. In addition, adrenal insufficiency, defined as an increment of serum cortisol levels after 1-mcg ACTH stimulation test of less than 9 mcg/dL[13] was also included in the analysis. Written informed consent was obtained from legal guardians of all participants. The study was approved by the Ramathibodi Hospital Ethics Committee (MURA 2013/12).

Statistical analysis

Data analysis was performed using the SPSS version 16.0 (SPSS Inc., Chicago, USA). Continuous variables are presented as mean (SD) or median (interquartile range, IQR). Differences between the two groups were assessed using the Chi-square test or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. Correlations between serum 25-OHD levels and basal, peak and increment of serum cortisol levels after 1-mcg ACTH stimulation test, as well as other continuous variables were evaluated by Spearman correlation. The *p*-value of less than 0.05 was considered statistically significant.

Results

There were 32 children with critical illnesses. Thirty-six healthy children served as controls. Means (SDs) ages of the patients and controls were 79 (61) and 92 (40) months, respectively. Seventeen patients and 16 controls were male. Age and sex were not different between the patients and controls. Median (IQR) PRISM III scores of the patients was 6.5 (2-12). No patients received vitamin supplementation prior to the admission. Twenty-three out of 32 children had preexisting diseases. Preexisting diseases in these patients included congenital heart disease (e.g. tetralogy of Fallot), hematologic malignancy (e.g. leukemia), neurologic (e.g. spinal muscular atrophy), genetic, renal and orthopedic diseases. Children in the control group did not receive vitamin supplementation. Mean (SD) duration of sunlight exposure of the controls was 91 (45) minutes per week. Characteristics of the patients and controls as well as their 25-OHD levels were summarized in Table 1. Of 32 children with critical illness, their median (IQR) serum 25-OHD level was significantly less than that of the control children (16.6 (13.3-19.5) vs. 24.2 (21.0-27.9) ng/mL, $p<0.001$). The proportion of children with vitamin D insufficiency

and deficiency altogether were greater in children with critical illness (Table 1). None of the critically ill children had vitamin D sufficiency (25-OHD of 30 ng/mL or greater), whereas seven of the healthy controls had vitamin D sufficiency. The odds ratio for vitamin D deficiency in the critically ill children compared with the healthy controls was 14.8 (95% CI, 4.6-48.0).

The summary of critically ill children with and without vitamin D deficiency is presented in Table 2. Compared between critically ill children

Table 1. Characteristics and vitamin D status of critically ill children and controls

Characteristics	Patients (n = 32)	Controls (n = 36)	*p*-value
Age (months)*	79 (61)	92 (40)	0.311
M/F, n	17/15	16/20	0.475
25-OHD (ng/mL)	16.6 (13.3-19.5)	24.2 (21.0-27.9)	<0.001
Vitamin D status, n (%)			<0.001
Deficiency (25-OHD <20 ng/mL)	25 (78)	7 (19.5)	
Insufficiency (25-OHD 20-29.9 ng/mL)	7 (22)	22 (61.0)	
Sufficiency (25-OHD ≥30 ng/mL)	0 (0)	7 (19.5)	
Illness required ICU admission, n (%)			
Sepsis	12 (37)	N/A	
Respiratory failure	8 (25)	N/A	
Sepsis and respiratory failure	4 (13)	N/A	
Hypertensive crisis	1 (3)	N/A	
Major post-operative care	7 (22)	N/A	

25-OHD = 25-hydroxyvitamin D; M = male; F = female; ICU = intensive care unit; N/A = not applicable
Data are presented as *mean (SD) or median (IQR), otherwise as indicated

Table 2. Comparisons between critically ill children with and without vitamin D deficiency

Parameters	Vitamin D deficient (25-OHD <20 ng/mL) (n = 25)	Non-vitamin D deficient (25-OHD ≥20 ng/mL) (n = 7)	*p*-value
Age (months)	60 (23-149)	33 (12-100)	0.151
M/F, n	14/11	3/4	0.538
25-OHD level (ng/mL)	15.2 (11.5-17.0)	21.7 (20.2-22.4)	<0.001
Total calcium (mg/dL)	8.8 (8.1-9.3)	9.1 (8.6-9.7)	0.312
Hemoglobin (g/dL)	10.6 (9.1-12.2)	10.9 (10.3-11.6)	0.820
Creatinine (mg/dL)	0.6 (0.4-0.8)	0.5 (0.3-0.7)	0.646
Albumin (g/L)	24.9 (22.5-31.9)	33.8 (25.1-36.0)	0.187
C-reactive protein (mg/L)	10.8 (3.8-88.2)	16.3 (8.7-23.9)	0.766
Basal cortisol (mcg/dL)	24.5 (17.7-46.2)	15.3 (10.9-29.9)	0.245
Peak cortisol (mcg/dL)*	35.4 (22.7-58.5)	37.0 (23.3-46.8)	0.698
Increment of cortisol (mcg/dL)*	9.5 (2.9-15.2)	9.0 (8.4-15.0)	0.386
Cortisol binding globulin (mg/L)	30.3 (23.6-36.8)	34.3 (26.9-41.1)	0.305
PRISM III score	7 (2-13)	5 (0-12)	0.450
Shock, n	10	3	0.892
Vasopressive drug use, n	6	2	0.805
Length of ICU stay (days)	6.0 (1.5-13.5)	3.0 (1.0-14.0)	0.479
Length of ventilator use (days)	4.5 (1.5-10.5)	3.3 (2.0-3.5)	0.422
Septicemia, n	4	0	0.258
Deceased, n	6	0	0.150

25-OHD = 25-hydroxyvitamin D; M = male; F = female; PRISM = Pediatric Risk of Mortality; ICU = intensive care unit
Data are presented as median (IQR), otherwise as indicated
* Peak cortisol and increment of cortisol were derived from 1-mcg adrenocorticotropic hormone stimulation test

with vitamin D deficiency (n = 25) and those without vitamin D deficiency (n = 7), their age, gender, preexisting disease, serum total calcium, creatinine, albumin and C-reactive protein levels and hemoglobin were not different. The median (IQR) PRISM III scores were not different between patients with and without vitamin D deficiency (7 (2-13) vs. 5 (0-12), respectively, $p = 0.450$). In addition, proportions of patients with shock and vasopressive drug use as well as their length of ICU stay and length of ventilator use were not different. However, all septicemic (n = 4) and all deceased (n = 6) children were vitamin D deficient. The median (IQR) serum 25-OHD level of non-survivors was significantly less than that of the survivors (12.2 (6.8-15.7) vs. 16.9 (14.9-20.1) ng/mL, respectively, $p = 0.026$).

Owing to the recommendation of the Institute of Medicine, serum 25-OHD cut-off level of 12 ng/mL is the lower threshold for adequate vitamin D requirement and this level is associated with risk of deficiency symptoms[18]. Therefore, the authors chose the serum 25-OHD level of 12 ng/mL for the additional analysis. Patients with serum 25-OHD level of less than 12 ng/mL (n = 6) and those with 25-OHD level of 12 ng/mL or greater (n = 26) were compared. The group of patients with lower serum 25-OHD levels had higher median (IQR) PRISM III score (14 (6-20) vs. 5 (2-10), $p = 0.033$) and higher proportion of mortality (3 out of 6 vs. 3 out of 26, $p = 0.030$).

The adrenal function in terms of basal and peak cortisol levels after 1-mcg ACTH stimulation test and its increment was not different between vitamin D deficient and non-vitamin D deficient groups. The medians (IQRs) serum 25-OHD levels of patients with (n = 8) and without (n = 24) adrenal insufficiency, defined as random serum cortisol level at admission of less than 15.1 mcg/dL[16], were not significantly different (18.2 (15.2-21.4) vs. 16.3 (11.2-19.2) ng/mL, respectively, $p = 0.139$). In addition, the medians (IQRs) serum 25-OHD levels of patients with (n = 15) and without (n = 17) adrenal insufficiency, defined as an increment of serum cortisol levels after 1-mcg ACTH stimulation test of less than 9 mcg/dL[13], were also not significantly different (16.9 (13.2-19.5) vs. 16.2 (12.8-19.7) ng/mL, respectively, $p = 0.692$). The adrenal function of patients with 25-OHD levels of less than 12 ng/mL and of those with 25-OHD levels of 12 ng/mL or greater was not different.

There were no correlations between serum 25-OHD levels and PRISM III score, length of ICU stay, length of ventilator use, serum albumin, C-reactive protein, cortisol binding globulin, basal cortisol, peak cortisol and increment of cortisol levels. Positive correlation between serum 25-OHD levels and total calcium was found (Table 3).

Table 3. Correlations between serum 25-hydroxyvitamin D levels and other variables

Variables	*r*	*p*-value
Total calcium	0.62	0.006
Albumin	0.32	0.093
C-reactive protein	-0.05	0.852
Basal cortisol	-0.17	0.362
Peak cortisol*	-0.13	0.492
Increment of cortisol*	0.04	0.847
Cortisol binding globulin	0.28	0.121
PRISM III score	-0.25	0.171
Length of ICU stay	-0.09	0.635
Length of ventilator use	0.07	0.744

PRISM = Pediatric Risk of Mortality; ICU = intensive care unit

* Peak cortisol and increment of cortisol were derived from 1-mcg adrenocorticotropic hormone stimulation test

Discussion

The present study demonstrated that a high proportion (78%) of critically ill children had vitamin D deficiency. This proportion was greater than that of the control children who were enrolled during the same period of time. In addition, 7 out of 32 critically ill children had insufficient vitamin D status (25-OHD level of 20-29.9 ng/mL). This is in agreement with previous studies that reported high prevalence of vitamin D deficiency in critically ill children[5,7,10,11]. McNally et al[7] reported that 69% of critically ill children admitted to ICU had serum 25-OHD levels of less than 20 ng/mL, and an additional 23% had serum 25-OHD levels between 20-30 ng/mL, which percentages were comparable to the authors' study (Table 1). The other studies[5,10,11] reported the prevalence of having serum 25-OHD levels of less than 20 ng/mL at 40%, 35% and 30% in their critically ill children, respectively, which were less than those of McNally's and the present studies. Use of multivitamin supplementation in participants of those studies may partly explain the lower rate of vitamin D deficiency in their studied patients. Several adult studies also reported high prevalence of vitamin D deficiency among critically ill patients, ranging from 38 to 97%[3,4,6,8,9].

Low serum 25-OHD levels in critically ill patients may reflect either pre-admission vitamin D status or its reduction during acute illness[4,5]. Critically ill patients often suffer from chronic conditions and have limited sunlight exposure, and may receive medications that alter vitamin D metabolism. These factors render them at high risk for vitamin D deficiency. However, the present study and most of the previous studies did not have pre-admission serum 25-OHD levels of the patients. The presence of preexisting chronic illnesses in most of the patients in the present study may prevent them from having adequate vitamin D status. Furthermore, there have been reports of reduced serum 25-OHD levels in patients with acute illness. Several mechanisms have been proposed. These included fluid administration, increased turnover and cellular uptake of 25-OHD, transcapillary leakage, and loss of vitamin D-binding protein concentration[19-21]. The authors' original study was not designed to determine the causality of vitamin D deficiency; therefore, these data were not available.

It has been reported that vitamin D deficiency was associated with poor outcome of critical illness. Braun et al[3] demonstrated that pre-admission vitamin D deficiency was a strong predictor for ICU mortality. Adult and pediatric studies have demonstrated the relationship between vitamin D deficiency in critically ill patients and severity score, length of ICU stay, fluid administration, catecholamine requirement, and mortality[3-7]. The mechanism by which vitamin D deficiency contributes to poor outcome in this group of patients remains unclear. The relationship may be related to pleiotropic functions of vitamin D in modulating immune system[22,23], producing anti-microbial peptide[24], augmenting cardiac contractility, gas exchange, and endothelial function[25]. In contrast, the present study did not reveal the associations between vitamin D deficiency, defined as serum 25-OHD levels of less than 20 ng/mL, and either severity of illness assessed by PRISM III score, length of ICU stay or length of ventilator use. Similarly, Rippel et al[10] reported the lack of association between vitamin D deficiency and need for mechanical ventilation, hypotension, need for vasoactive support, ICU or hospital length of stay, Pediatric Index of Mortality (PIM) 2 score, and death. However, it is of interest to note that all septicemic and deceased children of the present study were vitamin D deficient. Moreover, higher median PRISM III scores and mortality in the studied patients with serum 25-OHD of less than 12 ng/mL were demonstrated. The serum 25-OHD cutoff level of 12 ng/mL is the level that the Institute of Medicine recommends as the lower end of threshold for adequate vitamin D requirement and below this level is associated with risk of deficiency symptoms[18]. Therefore, a beneficial effect of adequate vitamin D status in critical illness could not be excluded and there may be a critical level of 25-OHD during critical illness needed to demonstrate its favorable effect, if any.

Adrenal insufficiency has frequently been reported in critically ill patients and it can cause hemodynamic instability. Adrenal insufficiency was associated with increased requirement of fluid resuscitation and increased use of vasopressor and mechanical ventilation[12,13]. Therefore, both adrenal insufficiency and vitamin D deficiency were associated with unfavorable outcome of critical illness[3,4,7,12,13]. In addition, vitamin D may modulate the glucocorticoid effects on cardiovascular system[15]. However, the association of adrenal insufficiency and vitamin D deficiency has not been established. In the present study, the authors did not find any associations between adrenal function and serum 25-OHD. This finding agrees with the result of a recent pediatric study that revealed no association between adrenal insufficiency and vitamin D status[14]. However, that study demonstrated an association between adrenal insufficiency and catecholamine use at the serum 25-OHD level of less than 12 ng/mL.

The strength of the present study is that it emphasizes a high proportion of vitamin D deficiency in the critically ill children by comparing with the much lower proportion of vitamin D deficiency in the healthy children enrolled at the same period of time. In addition, the present study reported the data on the relationship of vitamin D deficiency and adrenal function in pediatric critical illness which there has been only one report that the authors are aware of[14].

However, the authors acknowledge limitations of the present study. First, a small number of patients were recruited. The lack of difference may be partly due to being underpowered. Second, the present study was a secondary analysis of the previously published study, therefore some relevant data such as duration of sunlight exposure of the patient group, parents' education, were not available. Third, none of the critically ill children had vitamin D sufficiency (25-OHD of 30 ng/mL or greater); therefore an association between vitamin D deficiency and adrenal function, if any, may not be demonstrated. Fourth, the diagnostic criteria for diagnosis of adrenal insufficiency

in critically ill children are controversial; therefore, the comparison among studies was difficult.

Conclusion

The present study demonstrated a greater proportion of vitamin D deficiency in the critically ill children as compared with that of the healthy children. Although, serum 25-OHD level was not associated with the factors associated with severity of illness and adrenal function, there may be a critical level of serum 25-OHD in influencing the critical illness outcome, i.e. 25-OHD level of less than 12 ng/mL. A further larger study is required to confirm this finding.

What is already known on this topic?

High prevalence of vitamin D deficiency has been reported in critically ill children. Vitamin D deficiency may be related to increased severity of illness and mortality in critically ill patients.

What this study adds?

The present study demonstrated a greater proportion of vitamin D deficiency in critically ill children as compared with that of the controls. Vitamin D status was not associated with adrenal function in critically ill children.

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Potential conflicts of interest

None.

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ภาวะขาดวิตามินดีและการทำงานของต่อมหมวกไตในผู้ป่วยเด็กที่เจ็บป่วยวิกฤต

มนัสวี ก่อวุฒิกุลรังษี, พัฒน์ มหาโชคเลิศวัฒนา, โรจนี เลิศบุญเหรียญ, ละออ ชัยลือกิจ, เปรมฤดี ภูมิถาวร

ภูมิหลัง: ข้อมูลเกี่ยวกับความสัมพันธ์ระหว่างภาวะขาดวิตามินดีและภาวะพร่องฮอร์โมนจากต่อมหมวกไตในผู้ป่วยเด็กที่เจ็บป่วยวิกฤตยังมีไม่มากนัก

วัตถุประสงค์: เพื่อศึกษาระดับวิตามินดีในผู้ป่วยเด็กที่เจ็บป่วยวิกฤต และศึกษาความสัมพันธ์ระหว่างภาวะขาดวิตามินดีและการทำงานของต่อมหมวกไต

วัสดุและวิธีการ: ผู้เข้าร่วมการศึกษาประกอบด้วยผู้ป่วยเด็กที่เจ็บป่วยวิกฤตจำนวน 32 ราย และเด็กปกติที่มีสุขภาพดีจำนวน 36 ราย ผู้เข้าร่วมการศึกษาทุกรายได้รับการตรวจวัดระดับ 25-hydroxyvitamin D (25-OHD) ที่บ่งบอกระดับวิตามินดีในเลือด ส่วนผู้ป่วยเด็กที่เจ็บป่วยวิกฤตได้รับการเก็บข้อมูลเพิ่มเติม ดังนี้คือ คะแนน Pediatric Risk of Mortality (PRISM) III และผลการรักษาการเจ็บป่วยวิกฤต ผู้เข้าร่วมการศึกษาทุกรายได้รับการประเมินการทำงานของต่อมหมวกไตด้วยการตรวจทดสอบด้วยฮอร์โมน adrenocorticotropic ขนาด 1 ไมโครกรัม

ผลการศึกษา: กลุ่มผู้ป่วยมีค่ามัธยฐาน (พิสัยระหว่างควอร์ไทล์) ของระดับ 25-OHD ในเลือดต่ำกว่ากลุ่มเด็กปกติ (16.6 (13.3-19.5) และ 24.2 (21.0-27.9) นาโนกรัม/มิลลิลิตร ตามลำดับ ค่า $p<0.001$) พบภาวะขาดวิตามินดีในผู้ป่วยจำนวน 25 ราย (ร้อยละ 78) และในเด็กปกติจำนวน 7 ราย (ร้อยละ 19) ผู้ป่วยที่มีและไม่มีภาวะขาดวิตามินดีมีคะแนน PRISM III อัตราการเกิดภาวะช็อก การใช้ยากระตุ้นการหดตัวของหลอดเลือด ระยะเวลาที่ได้รับการรักษาในหอผู้ป่วยวิกฤต และระยะเวลาที่ต้องใช้เครื่องช่วยหายใจตลอดจนการทำงานของต่อมหมวกไตไม่แตกต่างกัน ผู้ป่วยที่มีระดับ 25-OHD ในเลือดน้อยกว่า 12 นาโนกรัม/มิลลิลิตร เมื่อเทียบกับผู้ป่วยที่มีระดับ 25-OHD ในเลือดตั้งแต่ 12 นาโนกรัม/มิลลิลิตร ขึ้นไป มีคะแนน PRISM III (14 (6-20) และ 5 (2-10) ตามลำดับ ค่า $p = 0.033$) และอัตราการตายมากกว่า

สรุป: การศึกษานี้พบภาวะขาดวิตามินดีในผู้ป่วยเด็กที่เจ็บป่วยวิกฤตมากกว่าเด็กปกติ และระดับ 25-OHD ในเลือดไม่มีความสัมพันธ์กับการทำงานของต่อมหมวกไต