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Burden and Outcome of Vitamin D Deficiency Among Critically Ill Patients: A Prospective Study

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Abstract

Background: Vitamin D deficiency is a prevalent condition among critically ill patients. Information about the relationship between vitamin D levels and outcomes in the intensive care unit (ICU) is sparse. *Purpose:* To evaluate vitamin D status among critically ill patients and its relevance to severity of illness, ICU stay period, and mortality. *Methods:* This prospective multicenter study was conducted in the ICUs of Fayoum, Cairo, Alazhar, and Ain Shams university hospitals. All patients were subjected to interview questionnaire, laboratory investigation, vitamin D level assessment, and severity of illness evaluation using the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score. *Results:* In total, 250 patients were included in the study. The median age was 62 (40–73) years, and most patients were male (52%). The median serum level of vitamin D was 19 (7–40.6). Vitamin D was deficient in 197 patients (78.8%) on admission. While we grouped the ICU patients as vitamin D deficient, insufficient, and sufficient, vitamin D–deficient patients had more severe diseases (mean APACHE II score, 44 ± 15; $P = .014$). Prolonged ICU stay was observed among the deficient group but with no significant association. The overall mortality rate was 6.8%; of these, 70.5% were vitamin D–deficient patients. However, logistic regression analysis demonstrated that vitamin D deficiency was not an independent risk factor for mortality. *Conclusion:* Vitamin D insufficiency is common in critically ill patients (69%); it is associated with more severity of illness, but it is not an independent risk factor for longer ICU stay or mortality. (*Nutr Clin Pract*.2017;32:378-384)

Keywords

vitamin D; mortality; hospital stay period; critically ill patients; vitamin D deficiency; critical illness; length of stay; intensive care units

Vitamin D is a fat-soluble vitamin that is converted in the body into biologically active metabolites, 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D. These metabolites regulate numerous functions in a variety of cell types. The key role played by vitamin D together with calcium in bone health is well known.[1]

Since receptors for vitamin D have been discovered all over the body, the Endocrine Society recommended a serum 25(OH)D concentration of at least 30 ng/mL for optimal health benefits.[2] The vital role of vitamin D in the immune system has been recognized through its receptors, which are present in different immune cells, including activated CD4 and CD8 T cells, B cells, neutrophils, macrophages, and dendritic cells, as well as its role in regulating immunoglobulin production.[3] Vitamin D has been shown to have anti-inflammatory and antiproliferative properties, and its deficiency has been linked to mortality.[4]

Although the role of vitamin D in the prevention and control of skeletal disorders was established a long time ago, its association with nonskeletal chronic diseases became evident in the 2000s.[5] Those diseases include certain types of cancer, diabetes, cardiovascular diseases, hypertension, and metabolic syndrome.[6–8]

Different degrees of vitamin D deficiency affect as many as 1 billion people worldwide. This high prevalence of vitamin D deficiency in the general population leads to the concern that this deficiency might be of importance for the critically ill.[2,9]

Vitamin D deficiency is rarely considered or treated in critically ill patients. Also, the prevalence of vitamin D deficiency and its significance in intensive care units (ICUs) are still unknown and not well studied.[1,10]

The prevalence of 25(OH)D deficiency in critically ill patients has been reported to range from 17%–79%.[1,11,12]

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Vitamin D deficiency and its association with multiple health outcomes have been studied by a large number of observational studies and randomized controlled trials. Great debates exist about the role of the vitamin among critically ill patients, and most studies reported that vitamin D is more likely to be a correlate marker of overall health and not causally involved in diseases.[5]

This study aims at evaluating the prevalence of vitamin D deficiency in ICU patients and correlating its level with patients' outcomes, which include disease severity, duration of ICU stay, and mortality.

Method

Setting and Duration of Work

The study was conducted in ICUs of Fayoum, Cairo, Alazhar, and Ain Shams university hospitals. The work was conducted throughout a 4-month period, from July 2013 through August 2013. It was also done during the same months in 2014 to control for any seasonal variation in the level of vitamin D concentration.

Study Design

A prospective analytical multicenter study was designed in which enrolled patients were followed up from the time of admission to ICU units until the time of occurrence of outcomes (discharge from ICU or death).

Sample Size and Patients

Sample size was calculated using EPICALC 2000 version (setting the prevalence at 80%, precision at 5%, and confidence interval at 95%), which yielded a sample of 245 patients. The study enrolled 250 patients. The only exclusion criterion was the patient being on vitamin D supplementation prior to the current admission. The recruited patients did not receive any vitamin D supplementation during the period of hospitalization.

Data Collection

After taking informed consent from the patients or their relatives, the recruited patients were subjected to a precoded interview questionnaire that included baseline demographic data (age and sex), the reason for admission, clinical assessment data, and laboratory investigation. The length of ICU stay was also recorded. The length of stay was defined as the time from ICU admission until the time of transfer out of the ICU. Although several scoring systems have been developed to grade the severity of illness in critically ill patients, the investigators applied the most commonly used: the second version of the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score introduced in 1985. It generates a point score ranging from 0–71 based on 12 physiologic variables, age, and underlying health. Also, it can calculate estimated mortality for every patient.[13]

Samples for serum total 25(OH)D and intact parathyroid hormone (IPTH) concentrations were withdrawn separately for the study purpose in the first 24 hours of ICU admission.

Samples were collected in plain tubes and covered with foil. After 15 minutes, they were centrifuged. Serum was separated in other tubes, and then all samples were kept in the deep freezer until the time of assay. Assessment of 25(OH)D was carried out by the second-generation platform of electrochemiluminescence (ECL) technology (Cobas 4111; Hitachi-Roche Diagnostics GmbH, Mannheim Germany). IPTH was assayed using the DXI 800 (Beckman Coulter, Brea, CA).

According to the Institute of Medicine, Food and Nutrition Board,[14] patients were classified into 3 groups based on vitamin D concentration as follows:

1. A healthy group with a level of vitamin D concentration >30 ng/mL (75 nmol/L)
2. An insufficiency group with a level of vitamin D concentration of 20–30 ng/mL (50–75 nmol/L)
3. A deficiency group with a level of vitamin D concentration <20 ng/mL (50 nmol/L)

Statistical Analysis

For each numeric variable, the normality of distribution was preliminarily assessed by the Kolmogorov-Smirnov test. Normally distributed variables were generally expressed as mean and standard deviation (SD). Abnormally distributed variables were expressed as median (25th quartile, 75th quartile). All qualitative data were presented as frequency and percentages. The relation of each variable with the outcome categories was separately tested by the χ^2 test for categorical variables, analysis of variance (ANOVA) with the post hoc test, or Mann-Whitney and Kruskal-Wallis tests for continuous variables. Correlation of vitamin D with other variables was tested by the Spearman test. To determine which combination of predictor variables led to the best predictive model, multivariate logistic regression analysis was carried out by using stepwise forward modeling (probability of F to enter = 0.05 and probability of F to remove = 0.10). The length of stay was dichotomized based on its median value (7 days) into 2 categories: short stay (≤7 days) and long stay (>7 days). All P values <.05 were considered significant. Data analysis was conducted using SPSS (version 15; SPSS, Inc, an IBM Company, Chicago, IL).

Ethical Consideration

The study design and method were approved by the Ethical Committee of the Department of Public Health, Cairo University. Data confidentiality was preserved throughout the study in accordance with the revised Helsinki Declaration of Bioethics. All

Table 1. Baseline Characteristics of the Patients Admitted to the Intensive Care Unit (ICU) (n = 250).

Patient Characteristic	Value
Age, median (IQR), y	62 (40–73)
Sex, No. (%)	
Male	130 (52)
Female	120 (48)
Diagnosis at time of hospital admission, No. (%)	
Medical	208 (83.2)
Surgical	42 (16.8)
APACHE II score, mean ± SD	32.9 ± 14.8
Estimated mortality, median (IQR), %	10.6 (4.7–27.1)
Length of ICU stay, median (IQR), d	7.0 (3.0–14)
Outcome, No. (%)	
Discharged	233 (93.2)
Died	17 (6.8)

APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; IQR, interquartile range.

Table 2. Distribution of Admitted Patients According to the Main Cause of Admission to the Medical Intensive Care Unit.

Cause of Admission	No. (%)
Myocardial infarction	70 (28.0)
Respiratory failure, pneumonia	33 (13.2)
Diabetic ketoacidosis	25 (10.0)
Sepsis and septic shock	25 (10.0)
Neurological affection (stroke and coma)	20 (8.0)
Gastrointestinal problem (liver disease, bleeding)	18 (7.2)
Other different causes	59 (23.6)

Table 3. Hematological and Biochemical Profile of the Patients Admitted to the Intensive Care Unit.

Laboratory Result	Value
Vitamin D level, median (IQR), ng/mL	7.6 (2.8–16.24)
Creatinine, median (IQR), mg/dL	1.01 (0.7–1.7)
Calcium, mean ± SD, mg/dL	7.6 ± 0.8
Phosphorous, mean ± SD, mg/dL	3.7 ± 1.54
IPTH, mean ± SD, pmol/L	7.88 ± 2.12
WBCs, median (IQR), 10^9/L	11.9 (8.7–17.5)
Corrected calcium, mean ± SD, mg/dL	8.8 ± 0.4

IPTH, intact parathyroid hormone; IQR, interquartile range; WBCs, white blood cells.

patients were informed about the aims of the study. Written informed consents were obtained from the participants or their relatives, who agreed to participate in the study.

Results

Basic Characteristics of the Patients

This prospective study enrolled 250 patients who were admitted to the ICU. Regarding the basic characteristics of the studied patients (Table 1), the age ranged from 18–88 years, and the median was 62 (40–73) years. For men, the median age was 61.5 (44.7–73) years, and for women, it was 63 (39–74.7) years (P = .602). Almost equal distribution of men (52%) and women (48%) was observed. Patients were admitted mainly for medical reasons (83.2%). The severity of score that was assessed by APACHE II ranged from 8–67, with a mean of 32.9 ± 14.8. The estimated mortality ranged from 0.7%–89.4%, with a median value of 10.6 (4.7–27.1). The length of ICU stay ranged from 1–50 days, with a median value of 7 (3–14) days. At the end of the study, 93.2% of the patients were discharged, while 6.8% died. Most patients (83.8%) were admitted for medical causes, and only a few cases were admitted for surgical ones. The main cause of admission is presented in Table 2.

IPTH values ranged from 2.0– 30 pmol/L with a mean of 7.88 ± 2.12 pmol/L (normal range, 1.3–9.3). The value of vitamin D concentration ranged from 2.8–39.12 ng/mL (Table 3).

Comparison of the 3 Groups

Patients were classified into 3 groups based on vitamin D concentration. The deficient group consisted of 197 patients (78.8%) with a median vitamin D level of 4 (2.8–10.2) ng/mL. The sufficient group consisted of 37 patients (14.8%) with a median level of 24.76 (18.28–27.69) ng/mL. The healthy group consisted of 16 patients (6.4%) with a median level of 35.32 (23.67–37.24) ng/mL (Figure 1). Among the deficient group, severe deficiency (vitamin D levels <5 ng/mL) was recorded in 51.2%, moderate deficiency (vitamin D levels 5–10 ng/mL) in 23.3%, and mild deficiency (vitamin D levels 10–20 ng/mL) in 25.5%. Comparison of the 3 groups of patients as shown in Table 4 revealed that the deficient group was significantly younger than the sufficient and healthy group (median age, 57, 66, and 73 years, respectively). Age comparison between each group revealed that the significant change was between the deficient group and the healthy group (P = .003).

No significant difference between groups was detected based on sex.

Vitamin D Concentration and APACHE II Score

The severity of illness was significantly higher among the deficient group, as indicated by the higher score compared with the other 2 groups, with the mean values of 44 ± 15, 33 ± 14.8, and 27 ± 13, respectively. Also, the estimated mortality was significantly higher in the deficient group (Table 4). However, the severity score and estimated mortality failed to show significant correlation with vitamin D concentration (r = 0.05, P = .56 and r = −0.02, P = .71, respectively). Post hoc test was applied

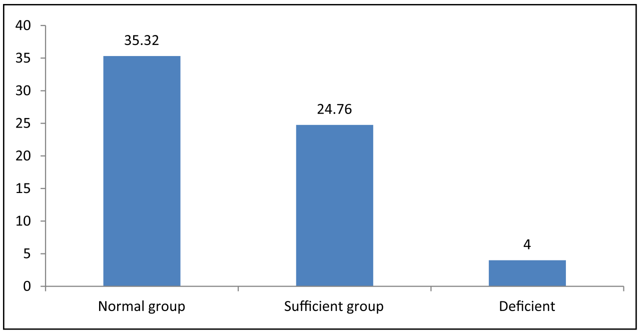

Figure 1. The median level of vitamin D (ng/mL) among the 3 groups of the patients admitted to the intensive care unit.

to demonstrate the significance between each group. It showed that the healthy group was significantly different from the other 2 groups.

Vitamin D and Prolonged ICU Stay

Despite the prolonged stay that was observed among the deficient group, no significant difference was detected (Table 4). The median level of vitamin D was 6.4 (2.8–14.32) ng/mL among patients with a prolonged stay and 8.08 (2.8–20) ng/mL among patients with a short stay ($P = .27$). The results of binary multivariate logistic regression are demonstrated in Table 5. It included age, sex, severity score, vitamin D level, and diagnosis. The significant predictors for long ICU stay length were the severity score and medical diagnosis ($P = .01$ and $P = .02$, respectively). Also, no significant correlation was found between vitamin D concentration and length of hospital stay ($r = -0.08$, $P = .27$).

Vitamin D Concentration and Mortality

The median level of vitamin D among deceased patients was 8 (2.8–29.8) ng/mL, while among the discharged, it was 7.6 (2.8–15.84) ng/mL. Binary multivariate logistic regression was done to detect the significant predictors of outcome. It included age, sex, severity score, and vitamin D concentration. The only significant predictor was the severity score ($P = .02$). This is demonstrated in Table 6. Significant changes were detected between each group and the other 2 groups.

Discussion

Vitamin D is a prohormone important for serum calcium and phosphorus homeostasis, which is crucial for proper neuromuscular function and skeletal health. Vitamin D can be obtained from food or made in skin after exposure to ultraviolet B radiation of the sun, which is the main source of vitamin D, with ample opportunities to form vitamin D during spring, summer, and fall. This study recruited patients during summer months in 2 consecutive years to control for seasonal variation. Vitamin D deficiency is likely to be common in hospitalized patients, especially among the critically ill.[15] Unfortunately, data regarding the relationship between vitamin D concentrations and outcomes of ICU patients are sparse.[16] However, with the rising concerns about the association between vitamin D concentration, inflammation, and sepsis, it was hypothesized that it has a role in the ICU. Thus, we aimed to assess the prevalence of vitamin D deficiency in ICU patients and to correlate its levels with patients' outcomes.

Our study showed that patients with 25(OH)D deficiencies were generally younger than patients with normal 25(OH)D levels and were mainly males. Most published studies show a higher prevalence of vitamin D deficiency in women and the elderly.[17,18] However, the large multicenter study by Braun et al[19] confirmed our association between low 25(OH)D levels and younger age but not with the male sex. Multiple studies have demonstrated that vitamin D deficiency is a common finding among critically ill patients.[20,21] In addition to the well-known risk factors for vitamin D deficiency, including age, living in northern latitudes, dark skin color, obesity, low dietary intake of vitamin D, and various medical conditions, especially malabsorption syndromes, other risks should be considered, especially in ICU-admitted patients, such as fluid resuscitation, gastrointestinal affliction, and interaction with medical treatment.[22]

Our study showed that the prevalence of vitamin D deficiency was 78.8%. This finding is consistent with other studies that reported the prevalence to be 82.3%, 77.8%, and 80.4%.[23–25]

A higher level of vitamin D deficiency (96.1%) was reported by Long-Xiang et al,[26] who interpreted this figure by the fact that their study was conducted in winter, which has been associated traditionally with low vitamin D as the patients were not exposed to sunshine.

The contribution of vitamin D in the severity of illness has been studied. Our results illustrated a significant association between vitamin D deficiency and severity of illness as evaluated by APACHE II score, which may be attributed to the pleiotropic actions of vitamin D in different body functions, including immunity, endothelial and mucosal functions, and metabolic functions.[27,28] Also, the contribution of vitamin D deficiency to multiple-organ failures and occurrence of systemic inflammatory response syndrome play an important role in affecting the severity of illness in critically ill patients.[1] Similar results were deduced by Ginde et al[29] and Zivin et al,[30] while other studies demonstrated no significant association with the severity score, and this may be due to the small sample sizes of both studies, which were 130 and 156 patients, respectively.[23,26]

In the present study, the length of ICU stay was dichotomized into <7 and >7 days. Although a lower level of vitamin D was recorded among patients with a longer stay, the result failed to prove significance. Also, the only significant predictors for a longer stay as shown by the multivariate analysis

Table 4. Comparison of Patients' Demographic and Clinical Data Based on Their Vitamin D Level.

Patient Characteristic	Vitamin D Level: Deficient (<20 ng/mL) (n = 197; 78.8%)	Insufficient (20–30 ng/mL) (n = 37; 14.8%)	Healthy (30–100 ng/mL) (n = 16; 6.4%)	*P* Value
Age, median (IQR), y	57 (35–72)	66 (48–75.2)	73 (68–77.3)	.008[a,b]
Sex, No. (%)				
Male	102 (51.7)	22 (59.4)	6 (37.5)	.59[c]
Female	95 (48.3)	15 (40.6)	10 (62.5)	
Diagnosis, No. (%)				
Medical	157 (79.6)	35 (94.6)	16 (100.0)	.06[c]
Surgical	40 (20.4)	2 (5.4)	0 (0.0)	
APACHE II score, mean ± SD	44 ± 15	33 ± 14	27 ± 13	.014[d]
Length of ICU stay, median (IQR), d	7.0 (4.0–14)	5.0 (3.0–12)	5.0 (3.0–11)	.47[a]
Estimated mortality, median (IQR), %	25 (11–49)	11 (4.0–27)	6.0 (4.0–15)	.01[a,e]
Outcome, No. (%)				
Discharged	185 (93.9)	35 (94.6)	13 (81.2)	.21[c]
Died	12 (6.1)	2.0 (5.4)	3.0 (18.8)	

APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; ICU, intensive care unit; IQR, interquartile range.
[a]Kruskal-Wallis *H* test was used.
[b]Significant difference between deficient and normal groups by Mann-Whitney (*P* = .0001).
[c]χ^2 test was used.
[d]Analysis of variance test was used.
[e]Significant difference between deficient and normal groups by Mann-Whitney (*P* = .002).

Table 5. Multivariate Analysis for Predictors of the Intensive Care Unit Length of Stay.

Predictor	Exponential B (CI)	*P* Value
Age	0.99 (0.91–1.0)	.2
Sex	1.4 (0.7–2.8)	.3
APACHE II score	1.03 (1.0–1.06)	.01
Vitamin D deficiency	3.6 (0.8–16.2)	.1
Vitamin D insufficiency	2.4 (0.4–12.5)	.3
Vitamin D normal (reference)		
Diagnosis (medical)	3.4 (1.2–9.5)	.02
Constant	0.03	.007

APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II.

Table 6. Multivariate Analysis for Predictors of Mortality.

Predictor	Exponential B (CI)	*P* Value
Age	1.03 (0.99–1.1)	.15
Sex	1.0 (0.3–3.9)	.9
APACHE II score	1.1 (1.0–1.11)	.02
Vitamin D deficiency	0.6 (0.03–8.7)	.7
Vitamin D insufficiency	0.5 (0.08–3.5)	.5
Vitamin D normal (reference)		
Constant	0.001	.007

APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II.

were the severity of illness and medical cause for admission. Similar results were mentioned by Venkatram et al[24] and Aygencel et al.[31] On the contrary, McKinney et al[21] reported a significant association between longer ICU stay and low vitamin D level. They dichotomized the length of stay into <3 and >3 days so that 60% of their patients had a hospital stay of fewer than 3 days. Deficiency of 25(OH)D has been implicated in much adverse systematic manifestation such as sepsis, stroke, autoimmune disease, myocardial infarction, heart failure, and other organ failure that may increase mortality.[32–35] The increased mortality might be also due to changes in glucose and calcium metabolism as well as immune and endothelial cell dysfunction.[36] Furthermore, it amplifies the metabolic derangement that is commonly seen in critically ill patients.[37]

A great controversy exists among different studies that assessed the association of vitamin D deficiency and mortality. Some studies suggest an association between vitamin D deficiency and mortality in critically ill patients.[19,24] A recent Cochrane review of 50 randomized trials with 94,148 participants showed that vitamin D in the form of vitamin D3 seems to decrease mortality predominantly in elderly women.[38] The main strength of the study is their large patient population, which improves the reliability of the results. In a study done by Van den Berghe et al,[39] vitamin D levels were lower among nonsurviving critically ill patients. A similar finding was reported by Lee et al,[1] who revealed a 3-fold rise in mortality rate in vitamin D–insufficient patients compared with those who were sufficient, and by McKinney et al,[21] who revealed vitamin D insufficiency to be nearly twice as prevalent among nonsurvivors in the ICU than among the survivors. Our study exhibited a nonsignificant association and revealed that the only significant predictor of mortality was the severity score. Our finding is consistent with Cecchi et al,[40] who observed that vitamin D levels had no relevance to mortality. Long-Xiang et al[26] also concluded that no there was no difference whether in terms of 28-day survival or 90-day survival between deficient and normal levels of vitamin D, and the only independent risk factor for mortality in their study was APACHE II score. The results of Lucidarme et al[20] confirmed the previous findings. Nair et al[41] conducted a multicenter cohort study to examine the association between vitamin D levels and clinical outcome. They reported that vitamin D deficiency is not associated with increased mortality. The most recent meta-analysis study, conducted by Theodoratou et al,[5] identified 107 systematic literature reviews, 74 meta-analyses of observational studies of plasma vitamin D concentrations, and 87 meta-analyses of randomized controlled trials of vitamin D supplementation and proved that highly convincing evidence of the role of vitamin D and different negative outcomes does not exist.

Limitations of the Study

The overall low mortality rate makes it difficult to detect a difference in mortality in relation to the vitamin concentration. Single measurement of vitamin D did not allow monitoring of changes in vitamin level during the ICU stay. High prevalence of medical vs surgical ICU patients limits the ability to extrapolate the results to all ICU patients.

Conclusion

In our results, vitamin D deficiency is prevalent among critically ill patients admitted to the ICU. The patients were mainly medical ICU patients. Despite the significant association between vitamin D level and severity of illness, no significant association was detected between the level of vitamin D concentration and the length of ICU stay or mortality.

Recommendation

Further studies are recommended with a larger sample size to assess if there is a direct causation between vitamin D status and patient outcomes, especially hospital stay and mortality. Further studies are warranted to clarify whether vitamin D supplementation is beneficial among critically ill patients.

Statement of Authorship

E. Anwar, G. Hamdy, E. Taher, E. Fawzy, S. Abdulattif, and M. H. Attia equally contributed to the conception and design of the research; E. Anwar, G. Hamdy, E. Fawzy, S. Abdulattif, and M. H. Attia contributed to the collection of the data; E. Taher, E. Anwar, E. Fawzy, and S. Abdulattif contributed to the analysis of the data; and G. Hamdy, E. Taher, and M. H. Attia contributed to the interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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