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Vitamin D Level and the Association with Morbidity and Mortality in Critically Ill Patients: A Single-center Study

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ABSTRACT

Objective: The present study aims to evaluate vitamin D (Vit D) level in critically ill patients and to assess its level about morbidity and mortality.

Materials and Methods: This study was conducted in an intensive care unit (ICU). Vit D level was measured on admission, third and seventh day.

Results: Of the 62 patients, the median Vit D level at baseline and on the third and seventh days was 12.8 mcg/L, 8.35 mcg/L, and 9.30 mcg/L, respectively. Vitamin D level was low (<30 mcg/L) in 92% of patients at baseline and 97% on the third day. 23% of the studied patients developed a new site infection. No statistically difference in the Vit D level at baseline, or on the third or seventh day based on the presence of infection (p=0.556, p=0.404, p=0.439, respectively). The most commonly seen infections were ventilator-associated pneumonia (VAP) and catheter-related bloodstream infection (CRBSI). The growth of Acinetobacter baumannii was the most frequent. Vit D level (p>0.05) might not have a causal role in mortality (ICU, 30-day, and 6-month), and no correlation was found between them.

Conclusion: The level of Vit D was low. Our study did not show any relationship between mortality rates and Vit D level, but VAP and CRBSI were observed.

Keywords: *Acinetobacter baumannii*, critical illness, intensive care unit, mortality, new site infection, vitamin D

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INTRODUCTION

Vitamin D (Vit D) influences immunity, cell cycle and angiogenesis. Vit D has been observed to be related to multiple systemic disorders and morbidity and mortality (1, 2). Vit D deficiency is widespread in hospitalized patients and specifically among the critically ill (3–5). The incidence of Vit D deficiency has been noticed to be between 21% and 81% in these patients (4, 6, 7). This may cause immune and metabolic dysfunction and poor prognosis (8, 9).

Relation between Vit D deficiency and mortality in critically ill patients has been reported previously (10, 11). In research investigating a relationship between the Vit D level and ICU mortality in Turkey Vit D level was measured at admission (12–14). Serially Vit D levels were measured in this study. Sequential monitoring is desirable to demonstrate that a satisfactory vitamin D level has been attained. However, to our knowledge, there is no other study to date examining the baseline Vit D level and values measured while in the ICU and a possible relation with mortality in Turkey.

The objective of our trial was to assess the admission level of Vit D and changes observed while in the ICU and to investigate any relation with mortality. A secondary aim was to analyze the Vit D level and any relationship to new site infections.

MATERIALS and METHODS

This trial was carried out in an 18-bed medical ICU with an annual admission of approximately 1100 patients. This research was confirmed by the ethical committee for research studies of the Medical Faculty of Erciyes University (date: 25.09.2014, no: 2014/557).

Study participants were admitted to the ICU between November 2014 and December 2015. Conscious patients were informed about this study directly, and in other cases, the family was advised of the details. Patients or legally authorized relatives gave written informed consent. All eligible patients were screened for inclusion criteria during the study period: patients who were older than 18 years old age and who were staying in the ICU for >48 hours. Other exclusion criteria were as follows: 1) chronic renal failure, 2) chronic liver disease, 3) granulomatous diseases, 4) hereditary phosphate-related diseases, 5) vit D-resistant rickets, 6) oncogenic osteomalacia, 7) pregnancy, and 8) current use of any drug-related to bone metabolism.

Table 1. Patient baseline demographic and clinical characteristics

Variables	Total n=62	Low vit D level (<30 mcg/L) n=57	Normal vit D level (>30 mcg/L) n=5	p
Age, years (IQR)	55 (36–72)	57 (38–74)	41 (29–61)	0.289
Sex, n (%)				
Male	30 (48)	28 (49)	2 (40)	0.696
Female	32 (52)	29 (51)	3 (60)	
Reason for ICU admission, n (%)				
Respiratory failure	26 (42)	23 (40)	3 (60)	
Sepsis/septic shock	20 (32)	20 (35)	0	
Neurological disorder	5 (8)	5 (9)	0	–
Intoxication	5 (8)	4 (7)	1 (20)	
Trauma	3 (5)	2 (4)	0	
Other	3 (5)	3 (5)	1(20)	
Glasgow Coma Score (IQR)	12 (6–15)	13 (6–13)	8 (8–15)	0.792
APACHE II score (IQR)	13 (9–18)	13 (9–18)	12 (7–20)	0.707
SOFA score day 1 (IQR)	3.5 (2–7)	4 (2–5)	2 (0–6)	0.284
SOFA score day 3 (IQR)	2 (1–6)	2 (1–6)	2 (0–8)	0.979
SOFA score day 7 (IQR)	7 (3–12)	2 (0–5)	9 (0–0)	0.665
Calcium (mg/dL), (IQR)	8.20 (7.70–8.92)	8.20 (7.70–8.80)	8.06 (7.60–10.55)	0.887
Calcium, ionized (mmol/L), (IQR)	0.71 (0.54–0.80)	0.70 (0.55–0.80)	0.80 (0.36–0.88)	0.772
Phosphorus level (mg/dL), (IQR)	3.21 (2.76–3.97)	3.20 (2.75–3.85)	3.96 (2.74–4.55)	0.332
Albumin (mg/dL), (IQR)	3.20 (2.50–3.62)	3.20 (2.55–3.64)	2.60 (2.35–3.80)	0.569
Baseline CRP (mg/L), (IQR)	113.00 (28.00–178.00)	118.00 (37.75–189.50)	23.40 (16.25–37.25)	**0.042**
Baseline procalcitonin (ng/mL), (IQR)	0.63 (0.152–2.27)	0.75 (0.15–3.15)	0.25 (0.07–1.76)	0.380
Vasopressor usage, n (%)	14 (23)	14 (100)	0 (0)	0.208
Renal replacement therapy, n (%)	6 (10)	5 (80)	1 (20)	0.233
New site infection, n (%)	14 (23)	12 (86)	2 (14)	0.331
Invasive mechanical ventilation, n (%)	33 (53)	29 (88)	4 (12)	0.211
Length of ICU stay, (days) (IQR)	5 (3–9)	5 (3.5–9)	3 (2.5–15)	0.584
Length of hospital stay, (days) (IQR)	9 (9–15)	9 (5–15)	8 (6–15)	0.990
ICU mortality, n(%)	17 (27)	15 (88)	2 (12)	0.511
Hospital mortality, n (%)	22 (36)	20 (91)	2 (9)	0.826
30-day mortality, n (%)	24 (39)	22 (92)	2 (8)	0.951
6-month mortality, n (%)	28 (45)	26 (93)	2 (7)	0.809

APACHE: Acute Physiology and Chronic Health Evaluation; CRP: C-reactive protein; ICU: Intensive care unit; SOFA: Sequential Organ Failure Assessment; Vit D: Vitamin D; IQR: Interquartile range (25%–75%)

Patients demographic characteristics, admission Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score on days 1, 3, and 7; Glasgow Coma Scale (GCS) score, underlying diseases, admission reason to ICU, number of days on mechanical ventilation, renal replacement therapy use, length of ICU stay, length of hospital stay, new nosocomial infections and ICU and 6-month mortality rates were noted. Vit D replacement was not performed in ICU.

Laboratory Analysis

Blood samples to determine the Vit D level were drawn in the first 24 hours following ICU admission and were centrifuged at 2000 g for five minutes. The sera specimens were protected from light and stored at -80ºC until the analysis was performed. To measure serum Vit D 25-hydroxyvitamin D (25[OH]D) levels radioimmunoassay (Tandem Gold LC-MS/MS; Zivak Technologies, Boca Raton, FL, USA) were used.

Deficiency of Vit D was 25(OH)D <20 mcg/L, insufficiency as 20–29 mcg/L, and sufficiency as a measurement of 25(OH)D >30 mcg/L, in conformity with the guidelines of the Endocrine Society (15).

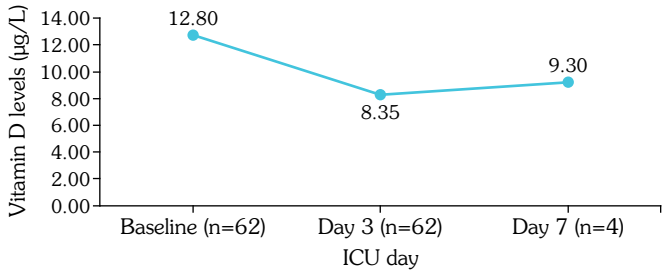

Figure 1. Baseline, third day, and seventh day median vitamin D levels

The median vitamin D level at baseline and on days 3 and 7 was 12.8 mcg/L (range: 2.80–104.0 mcg/L), 8.35 mcg/L (range: 1.80–96.30 mcg/L), and 9.30 mcg/L (range: 4.60–37.00 mcg/L), respectively (p>0.05)

Statistical Evaluation

SPSS, Version 22.0 (IBM Corp., Armonk, USA) was wont for the evaluation. The Shapiro-Wilk test, a histogram, and q-q plots were analyzed to evaluate the data normality. Levene's test was used for variance heterogeneity. A 2-sided independent samples t-test and the Mann-Whitney U test were used to compare groups. One-way repeated measures and the Friedman test were used for time comparisons. Additional analysis was administered using R version 3.0.2. R. P-value <5% was regarded as statistically significant. A Vit D level <30 mcg/L was accepted as the cut-off point for statistical investigation.

RESULTS

Of the 62 patients: 30 men (48%) and 32 women (52%) were contain in this study. The median age was 55 (IQR: 36–72) years. Demographics are provided in Table 1. Reason for ICU acceptance was respiratory insufficiency (42%) mostly, followed by sepsis/septic shock (32%). The median APACHE II score was 13 (IQR:9–18). The median Vit D level recorded at baseline and on days 3 and 7 was 12.8 mcg/L (min–max: 2.80–104.0 mcg/L), 8.35 mcg/L (min–max: 1.80–96.30 mcg/L), and 9.30 mcg/L (min–max: 4.60–37.00 mcg/L), respectively (p>0.05) (Fig. 1). In all, 80.6% were found to have a vit D deficiency at baseline and 88.7% on the third day. The Vit D insufficiency rate at baseline and on the third day was 11.3% and 8.1%, respectively. Low-level Vit D (<30 mcg/L) was determined in 92% at baseline and in 97% on the third day. The baseline CRP level was higher in patients with a low Vit D value compared with those who had a normal level (p<0.042) (Table 1). No statistically important correlation was observed between mortality and vitamin D level at baseline, days 3, days 7 (p=0.518, p=0.937, p=0.655, respectively). There was no statically association between 30-day mortality and Vit D level at baseline or on days 3 and 7 (p=0.750, p=0.1.00, p=0.655, respectively). No significant relation was found between 6-month mortality and Vit D level at baseline or on days 3 and 7 (p=0.872, p=0.906, p=0.700, respectively) (Table 2).

In addition, no statistically relation was determined between vitamin D level (baseline, days 3, days 7) and the presence of infection (p=0.556, p=0.404, p=0.439, respectively) (Table 3). Oral (n=11), enteral (n=16), parenteral (n=5), oral+enteral (n=1), and oral+parenteral (n=1) feeding routes were used. Nutrition delivery was initiated, on average 14 hours (range: 1–48 hours) after admission to the ICU. On average, 915 kcal/day (range: 400–2000 kcal/day) worth of nutrients was administered to patients on admission. 28 ICU patients were not fed during the first 48 hours.

Intermittent mechanical ventilation was required in 53% (n=33) with a median duration of two days (1–23 days). Vasopressor drugs were necessary for 23% (14 patients). The median hospital length of stay was nine days (2–45 days), while the median ICU length of

Table 2. Association between baseline, third-day, and seventh-day median vitamin D level and mortality

Variable	ICU mortality			30-day mortality			6-month mortality		
	Yes	No	p	Yes	No	p	Yes	No	p
Baseline (range) mcg/L	11.20 (3.0–104.0)	12.90 (2.8–56.5)	0.518	11.60 (3.0–104.0)	12.90 (2.8–56.5)	0.750	12.75 (3.0–104.0)	12.80 (2.80–56.5)	0.887
Day 3 (range) mcg/L	8.10 (3.0–96.3)	8.60 (1.80–29.2)	0.937	8.55 (2.6–96.3)	8.35 (1.8–29.2)	1.00	8.55 (2.6–96.3)	8.10 (1.8–29.2)	0.729
Day 7 (range) mcg/L	5.20 (4.6–37.0)	13.40	0.655	5.20 (4.6–37.0)	13.40	0.655	5.20 (4.6–37.0)	13.40	0.655

ICU: Intensive care unit

Table 3. Association between baseline, third-day, and seventh-day median vitamin D level and newsite infection

Variable	New site infection		
	Yes	No	p
Vitamin D baseline (range) mcg/L	14.10 (3.0–104.0)	12.5 (2.80–56.50)	0.556
Vitamin D day 3 (range) mcg/L	11.35 (2.60–96.30)	8.10 (1.80–29.20)	0.404
Vitamin D day 7 (range) mcg/L	21.10 (5.2–37.0)	9.00 (4.60–13.40)	0.439

Table 4. New site infections and microorganism (14 patients)

Patient	Infection site	Microorganism
1	Ventilator-associated pneumonia	No growth
2	Ventilator-associated pneumonia	*Staphylococcus aureus* (MSSA)
3	Ventilator-associated pneumonia	No growth
4	Ventilator-associated pneumonia	No growth
	Catheter-related BSI	Staphylococcus aureus (MRSA)
5	Ventilator-associated pneumonia	*Acinetobacter baumannii*
6	Ventilator-associated pneumonia	*Acinetobacter baumannii*
	Catheter-related BSI	Coagulase-negative *Staphylococci*
7	Ventilator-associated pneumonia	*Acinetobacter baumannii*
	Catheter-related BSI	Coagulase-negative *Staphylococci*
8	Catheter-related BSI	Carbapenem-resistant *Klebsiella pneumoniae*
	Catheter-related BSI	Coagulase-negative *Staphylococci*
9	Ventilator-associated pneumonia	*Pseudomonas aeruginosa*
	Catheter-related BSI	Coagulase-negative *Staphylococci*
10	Ventilator-associated pneumonia	*Pseudomonas aeruginosa*
11	Ventilator-associated pneumonia	No growth
	Urinary tract infection	No growth
12	Ventilator-associated pneumonia	*Acinetobacter baumannii*
	Urinary tract infection	*Klebsiella pneumoniae*
13	Hospital-acquired pneumonia	*Pseudomonas aeruginosa*
14	Catheter-related BSI	*Acinetobacter baumannii*
	Catheter-related BSI	*Pseudomonas aeruginosa*
	Urinary tract infection	*Enterococcus* species

BSI: Blood stream infection; MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA: Methicillin-susceptible *Staphylococcus aureus*

stay was five days (2–28 days). New site infections were observed in 14 (23%) patients during their ICU stay (Table 1).

The 23 infection episodes observed in 14 patients were VAP (n=12), CRBSI (n=8), urinary tract infection (n=2), and hospital acquired pneumonia (n=1) (Table 4).

The most commonly observed bacteria were Acinetobacter baumannii, Coagulase-negative Staphylococci, and Pseudomonas aeruginosa (n=5, 3, 3, respectively) (Table 4).

In summary, the ICU, hospital, 30-day, and 6-month mortality rates were 27%, 36%, 39%, and 45%, respectively (Table 1).There was no significant difference was seen between mortality (ICU, 30-day, 6-month) and Vit D level (p>0.05).

DISCUSSION

In patients with a normal absorptive capacity for Vit D, the circulating 25(OH)D level is sufficient to meet physiological needs. A 25(OH)D level of 20 ng/mL (50 nmol/L) has been recommended as a minimum for bone and mineral health in the general population (6) and 30–40 ng/mL (75–100 nmol/L) is required for muscle power and immunity (16, 17). Unfortunately, the minimum Vit D level has not yet been re-defined for critically ill patients, and general population definitions have been used for critically ill patients in most studies (6, 18). Therefore, we accept a 25(OH)D level of 30 mcg/L as the cut-off to define deficiency in our ICU patients.

This study showed that 80.6% of the patients were classified as Vit D deficient based on the baseline measurement, and 88.7% of the patients were deficient on the third day. The median Vit D level at baseline and on days 3 and 7 was 12.8 mcg/L (2.80–104.0 mcg/L), 8.35 mcg/L (1.80–96.30 mcg/L), and 9.30 mcg/L (4.60–37.00 mcg/L), respectively.

Venkatram et al. (18) investigated the relation between Vit D deficiency and mortality in a medical ICU in a retrospective trial of 437 patients. As in our study, Vit D deficiency was defined as 0–19.9 ng/dL, insufficiency as 20–29.9 ng/dL, and a normal level as ≥30 ng/dL. The authors reported a 25(OH)D deficiency rate of 77.8%, an insufficiency rate of 16.9%, and 5.3% with a normal level. The hospital mortality rate was higher in Vit D deficient patients. They also reported that the mean 25(OH)D vit level was higher in survivors (27.9±9.7 ng/dL) compared with dead patients (9.7±4.7 ng/dL) (p<0.0001). Their results were similar ours; however, we could not demonstrate any association between Vit D level and mortality, most likely because almost all of our patients were Vit D deficient and we had a smaller group of patients.

In an observational study of a mixed group of 1325 ICU patients, Braun et al. (19) evaluated the relationship between the Vit D level at admission and mortality. The mean Vit D level was 18.2±13.7 ng/mL. The in-hospital mortality rate was reported as 16.5%, while the 30-day, 90-day, and 365-day mortality rates were 17.2%, 24.2%, and 34.7%, respectively. Logistic regression analysis indicated that Vit D deficiency was a risk factor for mortality. In the present study, we also analyzed 30-day and 6-month mortality rates in our study group of ICU patients; however, the small number of patients and overall low levels may have contributed to the lack of a relationship in our results (Fig. 1).

The current data in the literature provide no consensus on these matters. For example, there is no single, agreed-upon, cut-off point and range to label Vit D deficiency. Therefore, the results of different studies vary (4, 10, 11, 20).

Vit D deficiency affects more than 70% of the US general population (6). The Vit D deficiency incidence has been reported to range from 21% to 81% in critically ill patients (4, 6, 7). Inconsistency in Vit D levels might be due to older age, less sun exposure, low dietary daily intake, or comorbidities (1, 21, 22). Age of the patients in our study was 53 years old, which is below the age considered geriatric; however, severe, chronic underlying diseases or comorbidities may have provided to the low Vit D level in our medical ICU patients. Second, a Vit D level measurement taken within 24 hours of admission shows preadmission insufficiency. Thus, we sampled the 25(OH)D level sequentially and followed up with subsequent Vit D measurements. It is expected that the 25(OH)D level would decline during an ICU stay since no supplements were provided, and sunlight exposure was also absent (21, 23).

We found that the level of 25(OH) D declined from 12.8 mcg/L to 8.35 mcg/L on the third day. Medication interactions, gastrointestinal dysfunction, and the resuscitation fluid load may also have been factors adding to the reduced value (22, 24).

Vit D plays a part in the regulation of the immune system (25), and insufficiency leads to immune dysregulation. Vit D deficiency results in increased susceptibility to VAP and sepsis (26, 27). In the present study, the CRP level was lower when the Vit D level was normal.

In our study, we found a rate of new site infection development of 23% in patients with low Vit D levels, and the most frequently observed were VAP and CRBSI.

Acinetobacter baumannii was the most commonly detected microorganism in our study.

The infection rate in patients group with low Vit D levels was slightly higher in a study carried out by Turkoglu et al. (28) in Turkey. They also reported the finding that Acinetobacter baumannii was the most frequent microorganism observed in patients with low Vit D levels (28).

A meta-analysis of 14 studies conducted between 2000 and 2014 carried out by Haan et al. (29) examined vitamin D level, infection, and mortality in 9715 patients with ICU. They concluded that there was an association between low Vit D level, severe infection, and mortality. Study shows that Vit D deficiency (<50 nmol/L) is associated with 30-day mortality and in-hospital mortality in adult critical care patients, in the globe (29).

Most studies suggest that the current support protocol is not adequate and high doses of Vit D have been found to restore sufficiency within several days. Daily 400–600 units of Vit D could be sufficient in standard nutritional support (30). Autier et al. (31) performed a metaanalysis about non-critically ill patients; supplementary doses of Vit D were associated with a 7% reduce in death rate. In our study, the Vit D level was higher on the seventh day than the third day after admission (p>0.05), which may be due to Vit D supplementation with standard enteral products.

Our study has some restrictions. This study was a single-center study with a small sample size; therefore, our results cannot be generalized. It was conducted in a medical ICU and cannot be generalized to cardiac, surgical, or other ICUs. Furthermore, the baseline, third and seventh-day Vit D levels were extremely low compared with normal levels.

In conclusion, Vit D deficiency was common at admission to the ICU and during follow-up in our medical ICU. Patients with low Vit D levels developed VAP and CRBSI. No significant association was detected between Vit D levels and mortality.

This study was present and published congress abstract book:
1. ESICM LIVES 2017" 30th Annual Congress, Vienna, Intensive Care Medicine Experimental 2017, 5(Suppl 2):0881 (Effect of vitamin D levels on mortality in critically ill patients: single center observational study) (https://icm-experimental.springeropen.com/track/pdf/10.1186/s40635-017-0151-4).

2. 40th ESPEN Congress, Madrid, Spain, 1–4 September 2018. Clinical Nutrition: September 2018, Vol. 37, S 284 (Vitamin D levels in critically ill patients on admission and during the ICU stay and its association with short and long term morbidity and mortality: A single center observational study) (https://www.clinicalnutritionjournal.com/article/S0261-5614(18)32272-6/fulltext).

Ethics Committee Approval: This research was confirmed by the ethical committee for research studies of the Medical Faculty of Erciyes University (date: 25.09.2014, no: 2014/557).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – KG, MS, GE; Design – MS, KG; Supervision – KG, GE, IHA, ZS, ST; Resource – MS, KG, MG; Materials – GE, ZS, İHA, ST; Data Collection and/or Processing – GE, ZS, IHA; Analysis and/or Interpretation – KG, MS, GE; Literature Search – GE, KG, ST; Writing – GE, KG, MS, ST; Critical Reviews – KG, GE, MS.

Conflict of Interest: The authors have no conflict of interest to declare.

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