ORIGINAL ARTICLE

The relationship between Vitamin D, clinical outcomes and mortality rate in ICU patients: A prospective observational study

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Background: According to the high prevalence of Vitamin D deficiency, a few studies have been conducted to clarify the relationship between 25-hydroxyvitamin D (25(OH)D) and clinical outcomes in critically ill patients. The objective of this study was to determine this probable association. **Materials and Methods:** Serum 25(OH)D, C-reactive protein, malnutrition measurements, and Intensive Care Unit (ICU)-acquired infection from 185 patients in ICU were assessed in the first 24 h of admission and they were followed for the other outcomes. **Results:** About 93.5% of patients were classified as deficient and insufficient while the others were categorized in sufficient group. 25(OH)D status was not significantly associated with mortality rate (P = 0.66), and no significant differences in ventilation time were observed (P = 0.97). Sufficient group left the ICU sooner, but the difference was not significant (P = 0.75). Besides the results of relationship between 25(OH)D concentration and nutritional status (P = 0.69) were not significant. In addition, sufficient group suffered from infection more than insufficient patients, but this relationship was not significant (P = 0.11). **Conclusion:** In this study, we found that 25(OH)D insufficiency is common in ICU patients, but no significant association between low 25(OH)D levels and ICU outcomes were observed. Hence, because of vital roles of Vitamin D in human's body, comprehensive study should conduct to determine the decisive results.

Key words: 25-hydroxyvitamin D, hospital-acquired infection, inflammation, Intensive Care Unit, length of stay, malnutrition, mortality, ventilation time

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INTRODUCTION

Vitamin D is a fat-soluble prohormone synthesized in the skin, or it is obtained from diet in small amounts[1] in spite of this fact the prevalence of Vitamin D deficiency is high among the population. This can be a reason of numerous difficulties such as skeletal and nonskeletal diseases.[2,3] The proposed mechanism for Vitamin D explained as affecting the calcium, magnesium and phosphate homeostasis in skeletal disease and regulating inflammation, cell proliferation, etc., in nonskeletal ones. It was reported in some studies that plasma concentrations of 25-hydroxyvitamin D (25(OH)D) is associated with C-reactive protein (CRP) concentrations in critically ill patients.[4] In addition, 25(OH)D may associate with mortality rate[5] but some studies reported that it is not an independent risk factor for it.[6] Researchers conducted studies to clarify the relationship between length of staying (LOS) in Intensive Care Unit (ICU) and serum 25(OH)D concentrations in ICU patients and they had reported an inverse association between them.[7,8] Besides increased acquired infection is proposed to be related to low serum levels of Vitamin D.[9]

Vitamin D has 4 stages including deficient (<10 ng/ml), insufficient (10–30 ng/ml), sufficient (30–100 ng/ml),

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and toxicity (>100 ng/ml). In spite of the fact that Vitamin D deficiency has high prevalence (more than 90%) in general population, this involves a great number of ICU patients.[10] It may be multifactorial in these patients and can affect sepsis procedure. Vitamin D receptors exist on immune cells. It has been reported that 1,25-dihydroxyvitamin D can inhibit the production of inflammatory markers.[11] In addition, because of inability to have appropriate response to trauma and infection the patients experience excessive LOS in ICU[7] and they may have levels of malnutrition during this time. Besides changes in glucose and calcium metabolism or immune and endothelial cell disorders may increase the mortality in patients with Vitamin D deficiency.[6]

The hypothesis of this study was to investigate that if Vitamin D deficiency was associated with poor clinical outcomes in critically ill patients. We expected that our results may be helpful to control the adverse outcomes in ICU patients through the promotion of enteral nutrition.

MATERIALS AND METHODS

This was a prospective observational study that assessed the relationship between serum 25(OH)D and clinical outcomes in 185 patients in ICU of the Al zahra Hospital in Isfahan from February to August 2015. Data collection was the first stage that lasted 7 months, and the patients were followed to the end of their staying in ICU to assess LOS in ICU, ventilation time, and 28 days mortality. In addition, serum 25(OH)D, CRP, malnutrition status, and the existence of ICU-acquired infection were assessed in the first 24 h of admission. The study protocol was approved by the Ethics Committee of Isfahan University Sciences (N: IR.MUI.REC.1394.2.101). We obtained written informed consent from all patients or their family members and their information was kept secret.

The purpose of this study was to use the Vitamin D in controlling the adverse outcomes in ICU patients. The inclusion criteria of the patients included all patients 18 years and older who expected to stay more than 24 h in ICU and need intensive cares. They were chosen in available form by nurses in the ICU. Patients whom receive special treatment which affected the results, pregnant patients and whom that had received Vitamin D supplements or multivitamins were not included in this study. Most of the included patients were traumatic, and the others suffered from cardiac, pulmonary neurological diseases, etc., Outcomes that were recorded included mortality, LOS, ventilation time, CRP, ICU-acquired infection, and malnutrition status. Age and sex were underlying factors and serum 25(OH)D was independent variable. For 25(OH)D measurement, Hitachi high-performance liquid chromatography 917 (sensitivity: 50 μg/l, imprecision <1%, and the accuracy is acceptable regarding a 95–105% recovery in standard reference material) was used, and the results were reported as ng/ml. The patients were divided into two groups: Sufficient (30–100 ng/ml) and insufficient (<30 ng/ml) levels of Vitamin D. Quantitative CRP was measured with Hitachi turbidimeter 902 and reported as mg/l. The used method was turbidimetric immunoassay. In addition, assess the mortality, ventilation time, ICU-acquired infection, and LOS were reported by information forms. ICU-acquired infection was defined as existing the septicemia or antibiotic consumption in first 48 h after admission in ICU.[9] Besides ventilation time was measured from the beginning of the ventilation to its end. For measuring the malnutrition percent, skin-fold thickness (TSF) were measured by caliper at triceps that was calibrated with Saehan Fat Caliper. Then, the mid-arm muscle circumference (MAMC) was calculated: MAMC = MAC (cm) – (3/14 × TSF [cm]). Mid-arm circumference (MAC) was measured using a nonstretch meter, without any pressure to body surface; measurements were recorded to the nearest 0.1 cm (Seca 201, Hamburg, Germany). Next, the percent of malnutrition was reported. If MAMC percent is up to 90 there is no malnutrition, 81–90 indicates mild malnutrition, 70–80 shows moderate, and below 70 categorizes as severe malnutrition.[12] These measurements were done by trained examiner. The patients divided into 3 groups named as severe and moderate malnutrition, mild malnutrition, and without malnutrition.[12]

The sample was collected in available form from the critically ill patient hospitalized in ICU. We considered the Type I error of 5% (α =0.05) and Type II error of 20% (β =0.20; power = 80%) and serum CRP levels as a key variable[4] and estimated the sample size about 185 patients.

No patients were lost to follow-up during the study.

All statistical analyses were done using the Statistical Package for Social Sciences, version 16 (SPSS Inc., Chicago, IL, USA) and the results were determined as descriptive and analytical form. Descriptive statistics for general characteristics of the study participants were reported. Two-independent *t*-test, one-way ANOVA, multiple linear, and logistic regressions were used for data analysis. Using multivariate models, age, sex, and other variables were adjusted in different models. Values are presented as frequency (percent), mean ± standard error, and interquartile range.

RESULTS

Patients and outcomes

In this study, 215 patients were enrolled but the analysis was done with 185 participants who completed the

survey [Figure 1]. The characteristics of the participants had been shown in Table 1. No Vitamin D deficiency signs or toxicity symptoms were observed in this study.

Our primary outcomes were serum 25(OH)D concentration, mortality rate, ICU-acquired infection, ventilation time, LOS, and CRP. Besides the relation between serum 25(OH)D concentration and malnutrition status, Vitamin D deficiency signs such as osteoporosis, osteomalacia, etc., and toxicity symptoms for example kidney stones, metastatic calcification of soft tissues, etc., are the secondary outcomes.

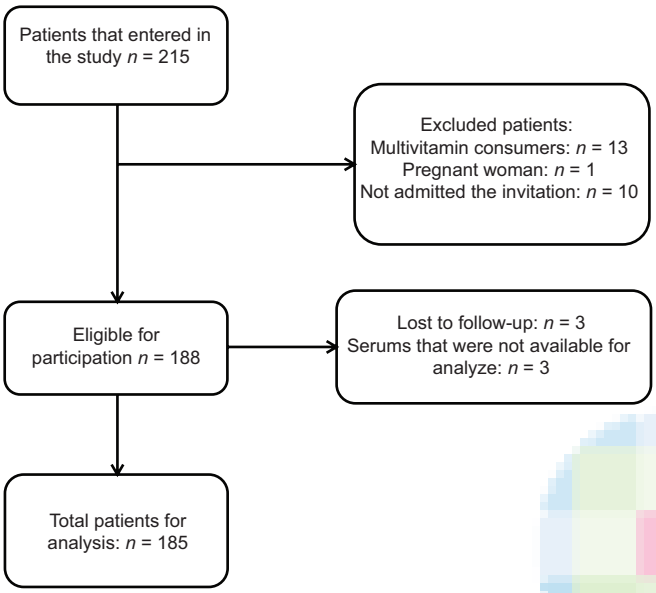

Figure 1: Flow diagram of study selection

The mean age of the participants was 55.60 ± 1.41 years. Based on the analysis, the mean concentration of 25(OH)D was 15.77 ± 0.66 ng/ml.

Effect of 25-hydroxyvitamin D levels on length of stay, infection, mortality, and malnutrition

In this survey, sufficient group left the ICU sooner but the difference was not significant (P = 0.75). Subsequent adjustments [Table 2], indicate that there was a reverse association between 25(OH)D concentration and LOS, but this relation was not significant.

The results of nosocomial infection indicated that the sufficient group involved with infection more than the patients with insufficient levels of Vitamin D but there was no significant relationship between two groups (P = 0.11). The confounders were adjusted in different models [Table 3] but no changes were observed. All-cause mortality was 12.7% in insufficient group while it was 16.7% in sufficient patients that the relationship was not significant (P = 0.66). In addition, using a multivariate Cox regression, different models were considered to clarifying the reliable results, but no changes were seen in the results [Table 3].

Patients had been followed for malnutrition and its relation with 25(OH)D concentration. The results indicate that the patients with the adequate concentration of

Table 1: Main characteristics of studied patients

	Total	Insufficient Vitamin D levels (<30 ng/ml)	Sufficient Vitamin D levels (30-100 ng/ml)	*P*
Numbers of patients	185	173 (93.5)	12 (6.5)	-
Sex (%)				
Male	95 (51.4)	91 (52.6)	4 (33.3)	0.24
Female	90 (48.6)	82 (47.4)	8 (66.7)	
Length of stay (day)	16.64±1.23 11 (6.5-20)	16.74±1.26 11 (7-21)	15.17±5.46 9 (6-12.75)	0.75
Ventilation time (day)	5.08±0.56 1 (0-7.5)	5.08±0.58 1 (0-7.5)	5±2.17 9 (0-9)	0.97
CRP (mg/L)	48.02±2.69 34 (15-85)	48.55±2.81 34 (15-85.5)	40.33±8.94 34 (13.75-57.5)	0.45
MAMC percent	89.89±0.5 91.5 (85.84-94.89)	89.83±0.52 91.5 (85.84-95.17)	90.62±1.87 92.51 (84.69-93.59)	0.69
Malnutrition levels (%)				
Severe and moderate	18 (9.7)	18 (10.4)	0 (0)	0.5
Mild	54 (29.2)	50 (28.9)	4 (33.3)	
Without	113 (61.1)	105 (60.7)	8 (66.7)	
Nosocomial infection (%)				
No	56 (30.3)	55 (31.8)	1 (8.3)	0.11
Yes	129 (69.7)	118 (68.2)	11 (91.7)	
Death (%)				
No	161 (87)	151 (87.3)	10 (83.3)	0.66
Yes	24 (13)	22 (12.7)	2 (16.7)	

Values are presented as mean±SD or frequency (%). CRP = C-reactive protein; MAMC = Mid-arm muscle circumference; SD = Standard deviation

Table 2: Relationship between 25-dihydroxyvitamin D concentration and outcomes: Length of stay, ventilation time, and mid-arm muscle circumference percent

Out comes	Crude model		Model 1		Model 2		Model 3		Model 4	
	B (SE)	*P*	*B* (SE)	*P*	*B* (SE)	*P*	*B* (SE)	*P*	*B* (SE)	*P*
LOS (day)	−0.096 (0.14)	0.49	−0.065 (0.14)	0.65	−0.079 (0.14)	0.58	-	-	-	-
VT (day)	0.002 (0.063)	0.98	−0.018 (0.064)	0.78	−0.020 (0.065)	0.75	-	-	-	-
MAMC (%)	0.078 (0.056)	0.16	0.062 (0.056)	0.27	0.032 (0.054)	0.55	0.031 (0.054)	0.57	0.024 (0.055)	0.67

LOS - Model 1 = Adjusted for age and sex; Model 2 = Adjusted for age, sex, malnutrition, CRP, infection; VT - Model 1 = Adjusted for age and sex; Model 2 = Age, sex, malnutrition, CRP, infection; MAMC - Model 1 = adjusted for age; Model 2 = Adjusted for age, sex; Model 3 = Adjusted for age, sex, LOS; Model 4 = Adjusted for age, sex, LOS, CRP, infection. LOS = Length of stay; VT = Ventilation time; MAMC = Mid-arm muscle circumference

25(OH)D had better nutritional status but this relationship was not significant (P = 0.69). After adjusting some confounders [Tables 2 and 3], we found that increased 25(OH)D levels were associated with the high percent of malnutrition, but this was not significant.

25-hydroxyvitamin D levels and ventilation time

The mean duration of ventilation time between two groups had no significant differences (P = 0.97). Some variables may have effect on ventilation time, so we adjusted them in models [Table 2]. The results indicated that there was inverse relationship between 25(OH)D levels and ventilation time, but this was not significant.

DISCUSSION

This observational study was carried out to evaluate the relationship between 25(OH)D concentration and clinical outcomes in 185 ICU patients. The results of this study showed low baseline 25(OH)D concentration in a significant number of ICU patients that confirm the previous studies. This was not the first survey to evaluate the relationship between Vitamin D concentration and ICU outcomes[13] but the large sample size of this study compared with the former ones may provide reliable results for future research. About 93.5% of patients in our study had insufficient status. Whereas 82% of participants in Higgins' *et al*. cohort,[9] 80.4% in Azim *et al*.'s study,[10] and 88% of patients in Barnett's survey had low baseline serum 25(OH)D. The high prevalence of Vitamin D deficiency in this study may be due to inadequate sun exposure, lack of Vitamin D food fortification program, clothing habits, polymorphism in Vitamin D receptors, and low daily calcium intake.[14,15] Because of key role of Vitamin D in vital functions of human body,[16-21] paying attention to this deficiency is necessary. Despite our study results, the effect of high prevalence of Vitamin D deficiency should not dissemble to improve the patient's status.

In thisstudy, the lack of association between mortality rate and Vitamin D status may be multifactorial. High prevalence of sepsis and antibiotic consumption were observed; therefore, the high number of infections may be an independent factor affecting the mortality rate. In agreement with this finding, the previous studies were reported no association between Vitamin D status and hospital mortality[6,10,13] However, it is demonstrated in a recent study that low Vitamin D levels are an independent risk factor for mortality in ICU.[22] Venkatram *et al*.[23] explained that Vitamin D receptors were expressed in many cells. Hence, Vitamin D can control the cell functions. In addition, increased in mortality rate in patients with insufficient status of Vitamin D may be due to changes in glucose and calcium metabolism and endothelial cell dysfunction. In other words, Vitamin D and its metabolites can modulate the endothelial stability and it was revealed that vascular instability is a sign of some inflammatory diseases. Therefore, prevention of its destabilization reduces pathology in some inflammatory diseases.[24] In addition, it has been shown in Arnson *et al*.'s study[21] that Vitamin D deficiency may play a role in many diseases that these are the reasons for increasing the mortality rate. It was mentioned in Amrein's cohort[25] that Vitamin D upregulates the production of which are active against many bacteria and fungi; thus, protecting the individual from infection and following events. Besides Braun *et al*.[5] illustrated that the relationship may be due to pleiotropic functions of Vitamin D. It inhibits vascular smooth-muscle cell proliferation and modulates inflammatory processes.

In this study, the sufficient group of Vitamin D patients left the ICU sooner but the difference was not significant. This finding is consistent with the Higgins' *et al*. study[9] which reported that low levels of Vitamin D are associated with longer time to ICU discharge. In additon, Matthews *et al*.[7] were shown the same results. In addition, an inverse association between 25(OH)D concentration and LOS was reported by Hélard *et al*.[8] Alizadeh *et al*.[13] confirmed the former surveys in 2015. Hence, the lack of relationship in this study may be due to our limitation such as selection bias or seasonal variations in sunlight exposure. Therefore, this failure should not be interpreted as evidence for lack of a true relationship, and the future research is necessary to find out reliable results.

No significant relationship was found between ICU-acquired infection and 25(OH)D concentration. It is in agreement with a prospective study[9] that reported nonsignificant

Table 3: Relationship between 25-dihydroxyvitamin D concentration and outcomes: Malnutrition, infection, and mortality

Out comes	Crude model			Model 1			Model 2			Model 3			Model 4			Model 5		
	B (SE)	Significant	OR (95% CI)	*B* (SE)	Significant	OR (95% CI)	*B* (SE)	Significant	OR (95% CI)	*B* (SE)	Significant	OR (95% CI)	*B* (SE)	Significant	OR (95% CI)	*B* (SE)	Significant	OR (95% CI)
Malnutrition																		
Severe-moderate	−0.14 (0.07)	0.07	0.87 (0.75-1.01)	−0.13 (0.07)	0.09	0.88 (0.76-1.02)	−0.11 (0.07)	0.13	0.89 (0.77-1.03)	−0.11 (0.07)	0.14	0.89 (0.77-1.04)	−0.11 (0.07)	0.14	0.89 (0.77-1.04)	−0.11 (0.07)	0.14	0.89 (0.77-1.04)
Mild	−0.01 (0.02)	0.45	0.98 (0.95-1.02)	−0.01 (0.02)	0.54	0.99 (0.95-1.03)	−0.01 (0.02)	0.83	0.99 (0.96-1.04)	−0.01 (0.02)	0.82	0.99 (0.96-1.04)	−0.01 (0.02)	0.82	0.99 (0.96-1.04)	−0.01 (0.02)	0.89	0.99 (0.96-1.04)
No malnutrition	-	-	1	-	-	1	-	-	1	-	-	1	-	-	1	-	-	1
Infection																		
Yes	−1.63 (1.05)	0.12	0.20 (0.03-1.55)	−1.63 (1.06)	0.12	0.20 (0.03-1.56)	−1.52 (1.06)	0.15	0.22 (0.03-1.74)	−1.56 (1.06)	0.14	0.21 (0.03-1.69)	−1.63 (1.07)	0.13	0.19 (0.024-1.6)	-	-	-
No	-	-	1	-	-	1	-	-	1	-	-	1	-	-	1	-	-	-
Death																		
Yes	−0.31 (0.80)	0.69	0.73 (0.15-3.55)	−0.37 (0.82)	0.65	0.69 (0.14-3.48)	−0.40 (0.83)	0.63	0.67 (0.13-3.41)	−0.42 (0.83)	0.62	0.66 (0.13-3.36)	−0.58 (0.84)	0.49	0.56 (0.11-2.92)	-	-	-
No	-	-	1	-	-	1	-	-	1	-	-	1	-	-	1	-	-	-

Malnutrition - Model 1 = Adjusted for age; Model 2 = Adjusted for age, sex; Model 3 = Adjusted for age, sex, LOS; Model 4 = Adjusted for age, sex, LOS, infection; Model 5 = Adjusted for age, sex, LOS, infection, CRP; Death - Model 1 = Adjusted for age; Model 2 = Adjusted for age, sex; Model 3 = Adjusted for age, sex, malnutrition, LOS; Model 4 = Adjusted for age, sex, malnutrition, LOS, CRP; Infection - Model 1 = Adjusted for age; Model 2 = adjusted for age, sex; Model 3 = adjusted for age, sex, LOS; Model 4 = Adjusted for age, sex, malnutrition, LOS, CRP. LOS = Length of stay; VT = Ventilation time; MAMC = Mid-arm muscle circumference; SE = Standard deviation; OR = Odds ratio; CI = Confidence interval

trend toward a higher number of infections. While this is in contrast with Braun *et al*.'s study[5] which mentioned that 25(OH)D deficiency is strongly associated with the risk of blood culture positivity. The proposed mechanism is that defects in macrophage functions, and the production of proinflammatory cytokines may occur in Vitamin D deficiency.

Ventilation time did not have a significant relationship with Vitamin D status in this study. This finding is consistent with Moraes' *et al*.[22] and Amrein *et al*.'s study[26] that found no significant differences in ventilation time. It was shown in Higgins' *et al*.[9] and Venkatram *et al*.'s,[23] the studies that no significant differences in ventilation days were evident among the groups. Besides these surveys, Matthews *et al*.[7] were reported that the patients were likely to have increased ventilation days but the significant results were not found. It is proposed that Vitamin D deficiency is associated with myopathy and decreased muscle strength. This may cause prolonged mechanical and sequential difficulties ventilation in ICU.[27]

In this study, we found no significant relationship between malnutrition status and 25(OH)D concentrations. It means that the patients with sufficient levels of Vitamin D had better nutritional status, and none of them was categorized in severe and moderate malnutrition group. Fraser[28] has mentioned that the decreased in Vitamin D binding protein (DBP), would decreased the ability to conserve 25(OH)D. Protein and energy deficiency decreased the DBP in blood plasma. Hence, the malnutrition may cause Vitamin D deficiency, but few studies were available in this field.

This study had several potential limitations. First, it was a single-center survey and the samples were collected only from one hospital. Second, the survey was conducted in winter and spring that the weak and limited exposure to sunlight could affect the results. In addition, some confounding factors such as type of disease that could bias the results were not considered. In addition, prehospital health conditions such as the body mass index that influencing the results were not considered.

Hence, more studies are needed to determine if there is direct relationship between Vitamin D status and patient outcomes in ICU. For this, larger studies are needed to access the reliable results.

Not only the wide population was considered in this study but also the few number of inclusion and exclusion criteria cause generalization the results to a larger community.

CONCLUSION

In this study, we found that 25(OH)D insufficiency is very common in the ICU patients and with due attention to Vitamin D key roles in vital routes in human's body, it is important to improve the Vitamin D levels in all age groups that suffer from Vitamin D deficiency. However, this prospective study showed no significant association between low 25(OH)D levels and ICU outcomes. Hence, comprehensive studies are needed to be done to clarify the Vitamin D benefits in ICU patients.

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTION

- NV contributed in the conception of the work, conducting the study, acquisition of data and drafting, approval of the final version of the manuscript, and agreed for all aspects of the work
- PK contributed in conducting the study and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- BA contributed in drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- AF contributed in analysis and interpretation of data for the work, approval of the final version of the manuscript, and agreed for all aspects of the work
- GHA contributed in the conception and design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.
- LA contributed in revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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