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Original Article

Is vitamin D deficiency associated with mortality in intensive care patients? An observational retrospective study

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Abstract

Aim: The objective of this study is to investigate effects of vitamin D levels in intensive care patients on length of stay in intensive care unit and duration of hospitalization, and the need for mechanical ventilation.

Material and Methods: This study was conducted as a retrospective study between February 2015 and January 2016. Length of stay in the intensive care unit and duration of hospitalization, and the need for mechanical ventilation were compared among all patients who were admitted to the intensive care unit and whose 25 (OH) D levels were examined. We further investigated whether vitamin D levels have an effect on 30-day mortality.

Results: A total of 155 patients were included in the study. Vitamin D deficiency was found in 123 (79%) patients, and vitamin D insufficiency in 21 (13%) patients, while vitamin D levels were evaluated as normal in the remaining 11 (7%) patients. The effects of 25(OH)D levels of the patients on the length of stay in the intensive care unit (P=0.302), duration of hospitalization (P=0.363), and the need for mechanical ventilation (P=0.150) were not statistically significant. No statistically significant difference was observed between the mortality rates according to vitamin D levels (P=0.377).

Conclusion: We found that 25 (OH) D vitamin levels were significantly low in intensive care patients. Although it is difficult to achieve a clear result because of a wide range of comorbidities in intensive care unit patients, we believe that further prospective randomized studies are warranted to clarify this issue.

Keywords: Vitamin D; Mortality; APACHE II; Intensive Care.

INTRODUCTION

25-hydroxyvitamin D [25 (OH) D] is a fat soluble vitamin which provides absorption of calcium and phosphorus from the intestines, and regulates calcium / phosphorus balance of the organism together with parathyroid hormone (PTH) (1).

A form of vitamin D storage, 25 (OH) D levels depends on the synthesis in the skin which is stimulated by ultraviolet rays and also on dietary intake of vitamin D containing compounds and nutritional supplement. 0.03% of 25 (OH) D vitamin is in free form and about 88% is bound to vitamin D binding protein (DBP), while the remaining part binds to albumin (2). 25 (OH) D vitamin is a parameter which provides the best information about entire vitamin D pool of the body, with a half life of 15 to 20 days (3). Vitamin D plays an important role in bone health and regulation of calcium metabolism, as well as in immune system, endothelial and mucosal structures, and glucose metabolism (4). The prevalence of vitamin D deficiency (25 (OH) D< 20 ng/mL) (5) is higher than 70% in critical patients (6). Low levels of 25 (OH) D are is associated with myocardial infarction, diabetes mellitus, autoimmune disease, chronic obstructive pulmonary disease, tuberculosis, and increased rate of mortality in general population (7), and with increased rate of infections,

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prolonged duration of hospitalization, excessive health spending, and high hospital mortality in intensive care patients (8).

The objective of this study was to investigate effects of vitamin D levels in of intensive care patients on length of stay in intensive care unit and duration of hospitalization, and the need for mechanical ventilation.

MATERIAL and METHODS

This study was conducted by retrospective evaluation of a database which was prospectively stored and medical records of all patients who were admitted to the intensive care unit of our hospital and whose 25 (OH) D were examined between February 2015 and January 2016. The study was approved by the local ethics committee of the hospital and each patient gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Patients aged over 18 years whose 25 (OH) D levels were studied during admission to the intensive care unit and who were treated in the ICU for longer than 48 hours were included in the study. Patients who were taken to the ward, and then admitted again to the intensive care unit were excluded from the study. Because there are no clear limits for the optimal 25 (OH) D levels, patient groups were defined in line with the previous studies. Patients were divided into three groups according to their 25 (OH) D levels after admission to the ICU. Patients with a 25 (OH) D<19.9 ng/mL were considered as having vitamin D deficiency, 25 (OH) D between 19.9 and 29 ng/mL as having vitamin D insufficiency, and 25 (OH) D > 30 ng/mL as normal (6). After admission to the intensive care unit, patients' demographic data (age, sex), history of chronic disease, and localizations before the admission to ICU [emergency room, hospital ward, another hospital, another ICU, operating room] were recorded.

Among the routine laboratory variables; albumin (g/dL), creatinine (ng/mL), calcium (mg/dL), phosphorus (mg/dL), leukocyte (g/dL), parathyroid hormone (pg/mL), procalcitonin (ng/mL), and 25 (OH) D vitamin levels (ng/mL) were evaluated within the first 24 hours of admission to the ICU. 25 (OH) D levels were evaluated with electrochemiluminescence (ECLIA) method (Elecsys assay on Roche Modular E170 analyzer, Roche Diagnostics, Germany).

Acute Physiology and Chronic Physical Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores of the patients were recorded. Acute Kidney Injury Network (AKIN) classification was carried out and recorded in the patients with renal failure.

Patients' length of stay in the intensive care (days), duration of hospitalization (days), and need for mechanical ventilation (days) were recorded.

Statistical analysis

Statistical analysis was performed using SPSS v 15 software. Normality of the variables was examined with Kolmogorov Smirnov test. Normally distributed variables were analyzed with t test, and expressed as mean ± standard deviation (SD). Non-normally distributed variables were analyzed using Mann Whitney U test. Categorical variables were analyzed with Chi-square Test and Fisher Exact Test, and expressed as frequency and percentage (%). Effects of vitamin D levels on survival were analyzed using log rank test. Survival rates were calculated with Kaplan-Meier survival analysis. The correlations between vitamin D levels and different parameters were analyzed with Spearman / Pearson correlation test. P values < 0.05 were considered statistically significant.

RESULTS

25 (OH) D level measurements were available in 164 (63.07%) of 260 patients who were admitted during the study period. Of these, 155 were included in the study, and 9 patients were excluded due to readmission to the intensive care unit.

25 (OH) D deficiency was found in 123 (79%) patients, and 25 (OH) D insufficiency in 21 (13%) patients, while 25 (OH) D level was considered as normal in 11 (7%) patients, and the mean 25 (OH) D levels of the groups were calculated as 8.73 ± 4.88, 23.44 ± 3.04, and 43.47 ± 8.24; respectively. The mean age of overall patients admitted to the ICU was 71.07 ± 16.77 years (F/M= 74/81). Whereas no statistically significant difference was found between APACHE II scores of the groups (P=0.26), there was a statistically significant difference in SOFA scores (P=0.013).

Comparison of the patients' clinical characteristics, AKIN classification, diagnosis of admission to the ICU, and localizations before the admission according to 25 (OH) D levels are shown in Table 1.

Effects of 25 (OH) D levels of the patients on length of stay in the ICU (P=0.302), duration of hospitalization (P=0.363), and the need for mechanical ventilation (P=0.150) were not statistically significant (Table 2).

No statistically significant difference was observed between 30-day mortality rates according to 25 (OH) D levels (P=0.377) (Figure 1).

The mean survival durations of the groups are given in Table 3.

Pearson correlation test revealed a moderate negative correlation was found between vitamin D level and APACHE II (Table 4).

Table 1. Comparison of clinical characteristics of patients according to 25 (OH) D vitamine levels

	Total (N=155)	25 (OH) D Deficiency ≤19.9ng/ml (N=123)	25 (OH) D Insufficiency 19.9-30 ng/ml (N=21)	25 (OH) D Normal >30 ng/ml N=11)	P Value
Age (years)	71.07±16.77	71.19±16.26	71.81±15.22	68.36±25.10	0.84
Gender - Male (%)	74/81	60/63	3/18	11/0	
Vitamin D (ng/mL)	13.19 ±10.96	8.73±4.88	23.44±3.04	43.47±8.24	0.001*
APACHE II	21.92± 7.00	22.39±7.30	20.00±5.42	20.36±5.75	0.26
SOFA	8.02 ±3.73	8.38±3.91	7.09±3.08	6.43±2.29	0.013*
Albumin (g/dL),	2.81 ±0.69	2.83±0.68	2.84±0.68	2.59±0.81	0.53
Creatinine (ng/mL)	2.54±2.69	2.39±2.20	3.48±4.36	2.52±3.48	0.22
Calcium (mg/dL)	8.36±0.84	8.31±0.85	8.59±0.65	8.45±1.07	0.37
Phosphorus (mg/dL)	4.74±2.90	4.98±3.13	3.62±1.15	4.30±1.98	0.12
Leukocyte (g/dL)	17.92±46.96	18.97±52.60	13.51±6.29	14.61±8.35	0.86
Parathyroid Hormone (pg/mL)	188.82±191.72	203.90±189.32	173.76±227.44	49.04±23.53	0.03*
Procalcitonin(ng/mL)	7.2±16.75	6.80±15.71	6.54±16.85	13±26.53	0.49
AKIN Classification					0.95
Stage I	49 (%31.6)	39 (%71.22)	6 (%28.57)	4 (%36.36)	
Stage II	27 (%17.4)	22 (%17.39)	4 (%19.05)	1 (%9.09)	
Stage III	20 (%12.9)	15 (%12.2)	4 (%19.05)	1 (%9.09)	
Diagnosis of admission to the ICU					0.14
Endocrine	3 (%1.93)	2 (%1.63)	1 (4.76)	0 (%0.00)	
Renal	26 (%16.7)	17 (%13.82)	6 (%28.57)	3 (%27.27)	
Cardiac	18 (%11.6)	17 (%13.82)	0 (%0.00)	1 (%9.09)	
Sepsis	32 (%20.6)	28 (%22.76)	3 (%14.29)	1 (%9.09)	
Trauma	11(%7.09)	10 (%8.13)	0 (%0.00)	1 (%9.09)	
Neurological	23 (%14.8)	18 (%14.63)	3 (14.29)	2 (%18.18)	
Metabolic / Gastrointestinal	12 (%7.7)	7 (%5.69)	5 (%23.81)	0 (%0.00)	
Respiratory	30 (%19.3)	24 (19.51)	3 (%14.29)	3 (%27.27)	
Localizations before the admiss ion to the ICU					0.27
Emergency room	106 (%68.3)	85 (%69.11)	12 (%57.14)	9 (%81.82)	
Hospital ward	6 (%3.87)	6 (%4.88)	0 (%0.00)	0 (%0.00)	
Another hospital	4 (%2.58)	3 (%2.44)	1 (%4.76)	0 (%0.00)	
Another ICU	37 (%23.87)	28 (%22.76)	8 (%38.1)	1 (%9.09)	
Operating room	2 (%1.29)	1 (%0.81)	0 (%0.00)	1 (%9.09)	

APACHE II; AcutePhysiologyand Chronic Physical Health Evaluation II. SOFA; Sequential Organ Failure Assessment scores. AKIN classification; Acute Kidney Injury Network. *P<0,05mean±SD

Table 2. Comparison of primer outcomes of patients according to 25 (OH) D vitamine levels

	Total (N=155)	25 (OH) D Deficiency ≤19,9ng/ml (N=123)	25 (OH) D Insufficiency 19,9-30 ng/ml (N=21)	25 (OH) D Normal >30 ng/ml (N=11)	P Value
Length of stay in the intensive care (days)	14.26±13.87	14.01±13.82	12.62±9.96	20.27±19.72	0.30
Duration of hospitalization (days)	16.75±15.20	16.50±15.48	15.10±10.42	22.82±19.27	0.36
Need for mechanical ventilation (days)	7.72±11.28	7.54±10.92	5.62±6.89	13.64±18.99	0.15

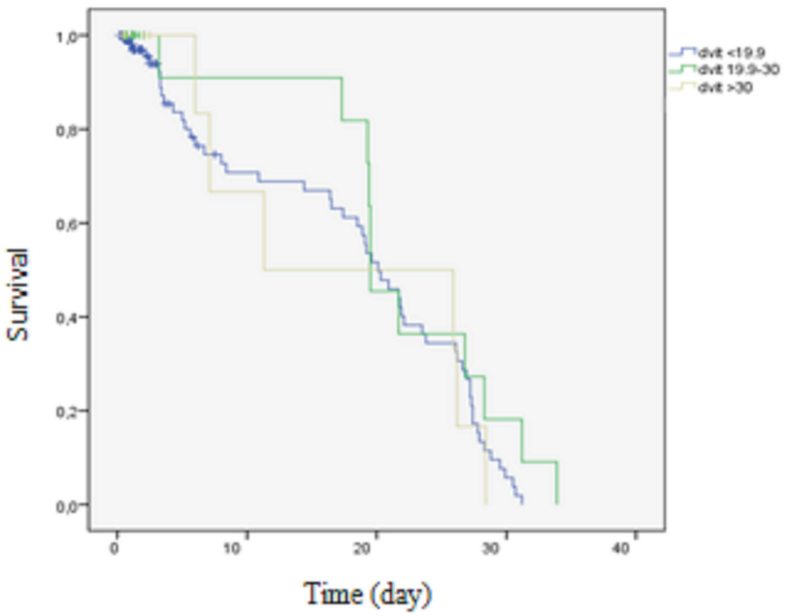

Figure 1.30 day mortality among the groups

Table 3. Average survival times of Groups

Group	Average time			
	Time (day)	SD	%95 Confidence Interval	
			Lower limit	Upper limit
D vit<19.9ng/dl	180.021	12.918	154.703	205.340
D vit19.9-30 ng/dl	218.273	25.060	169.154	267.391
D vit>30 ng/dl	174.833	42.580	91.377	258.289
Total	185.106	11.151	163.250	206.963

D vit; vitamin D, SD; standard deviation

Table 4. Pearson correlation table of some parameters with D vitamin level

	APACHE II	Albumin	Creatinine	Procalcitonin	Length of stay in the intensivecare	Duration of hospitalization	Need for mechanical ventilation	Vitamin D level
SOFA	PC 0.391** P 0.000	-0.205* 0.011	0.222** 0.006	0.236** 0.003	-0.065 0.425	0.008 0.918	0.143 0.076	-0.139 0.086
APACHEII		-.097 0.228	0.218** 0.007	0.302** 0.000	0.012 0.879	0.035 0.668	0.189* 0.018	-0.247** 0,002
Albumin			-0.097 0.228	-0.210** 0.009	-0.082 0.309	-0.179* 0.026	-0.063 0.436	-0.053 0.513
Creatinine				0.226** 0.005	-0.097 0.232	-0.058 0.475	-0.035 0.667	0.072 0.375
Procalcitonin					-0,062 0.446	-0.051 0.530	0.064 0.431	-0.091 0.258
Length of stay in theintensive care						0.887** 0.000	0.674** 0.000	0.126 0.117
Duration of hospitalization							0.611** 0.000	0.114 0.158
Need for mechanical ventilation								0.162* 0.044

PC; Pearson Correlation, P; P value, **Correlation was significant at P 0.01 level, *Correlation was significant at 0.05 levels

DISCUSSION

The results obtained indicate that 25 (OH) D deficiencies were found in 79% of patients who were admitted to the intensive care unit.

25 (OH) D deficiency is commonly encountered in intensive care patients with a prevalence reported between 17% and 79% in the literature (6,9). The prevalence and importance of vitamin D deficiency in these critical patients is yet to be fully understood. The reasons of low vitamin D levels in intensive care unit patients are multifactorial. These reasons may include elderly and immobilized patient population and deficiency of sunlight exposure (10). In addition, malnutrition, obesity, hepatic and renal failure, gastrointestinal dysfunction, and side effects of fluid replacement are among these reasons (11).

Our hospital delivery services at the middle class population whose average age is 71.07 ± 16.77. This group of patients poses a higher risk for the incidence of critical disease and hypovitaminosis.

We observed in our study that, 25 (OH) D levels that were evaluated at admission of our patients to the intensive care unit had no effect on the length of stay in the intensive care unit, duration of hospitalization, and the need for mechanical ventilation. There was a correlation between vitamin D levels and APACHE II scores, although vitamin D levels did not affect 30-day mortality.

Although many studies have underlined that vitamin D deficiency is higher among women and elderly (12,13), in our study vitamin D deficiency was common in both sexes, and even our patient group with normal vitamin D levels entirely consisted of female patients.

In the case of vitamin D deficiency, immune system and endothelial cell dysfunction secondary to the alterations in glucose and calcium metabolisms may lead to increased rates of mortality in intensive care unit (7). Endothelial cell dysfunction is also considered as a potential cause of multiorgan dysfunction syndrome (14). Similar to the study by Venkatram et al., we could not find a correlation between 25 (OH) D deficiency and length of stay in intensive care unit.

Intensive care unit patients usually have multisystem involvement, and vitamin D plays a role in many systems beyond the musculoskeletal system. Altough the fact of that underlying comorbidities will be the most important factors affecting mortality in intensive care unit patients can not be denied, but resolving vitamin D deficiency / insufficiency at least may improve the need for ventilation, decreasing hyperglycemia due to stress, and providing protection against renal dysfunction and bone resorption in critically ill patients (15).

In our study, it was observed that 25 (OH) D levels were not effective on 30-day mortality, and also no significant difference was found between the groups in terms of leukocyte count and procalcitonin levels.

Although serum phosphate levels are increased in chronic kidney failure due to the decreased renal phosphate excretion, conversion to 1-25 (OH)2 vitamin which is the active form of vitamin D is reduced, resulting in a decrease in serum calcium levels. Hyperphosphatemia, hypocalcemia, and decreased levels of active vitamin D cause increased synthesis and secretion of parathyroid hormone. Although vitamin D deficiency and hypocalcemia are highly common among intensive care patients, this interaction among calcium level – PTH concentration – vitamin D level is generally impaired (16). In our study, acute and/or chronic renal failures were found in 62.5% of patients with vitamin D deficiency / insufficiency, according to the AKIN classification. At the same time, PTH levels were found to be increased in order to compensate vitamin D deficiency which was commonly found in our patient group.

Although epidemiological studies recommend to keep serum 25 (OH) D level over 20 ng/mL in order to prevent diseases such as rickets and osteomalacia, and to maintain normal bone quality; it is recommended that 25 (OH) D level should be above 30 ng/mL in order to decrease the risk for chronic diseases such as cancer, autoimmune diseases, and cardiovascular diseases (3).

Braun et al. showed that 25 (OH) D deficiencies are strongly correlated with the risk of mortality in intensive care unit, and this risk is independent from the other risk factors, and stated that 25 (OH) D deficiencies are strongly associated with the risk of positive blood culture (10).

On the other hand, vitamin D deficiency has been stated to be not correlated with severe sepsis and septic shock outcomes (17).

An effect of vitamin D deficiency on the prognosis in intensive care unit patients is unclear. Some studies report that vitamin D deficiency is associated with increased rate of mortality (6,18,19), while the others report no such a correlation (20,21). Cecchi et al. (17) concluded that serum vitamin D levels have no significant effects on the results of septic patients. Effects of vitamin D replacement on mortality are controversial, but APACHE II score and the number of organ dysfunctions are still underlined as important parameters for increased rate of mortality. Sindhaghatta et al. reported a clear correlation between 25 (OH) D levels and hospital mortality rates in critical patients, and that hospital mortality observed in patients with vitamin D deficiency is higher than estimated rate according to APACHE IV score (6). In our study also, a correlation was observed between 25 (OH) D levels and APACHE II scores for predicting mortality.

The first limitation of our study is its retrospective design, and the second is that the study was not conducted in a specific patient group.

CONCLUSION

In conclusion, we found that 25 (OH) D vitamin levels were significantly low in intensive care patients.25 (OH) D levels that were evaluated at admission of our patients to the

intensive care unit, had no effect on the length of stay in the intensive care unit, duration of hospitalization, and the need for mechanical ventilation. There was a correlation between vitamin D levels and APACHE II scores, although vitamin D levels did not affect 30-day mortality. Although it is difficult to achieve a clear result because of a wide range of comorbidities in intensive care unit patients, we believe that further prospective randomized studies are warranted to clarify this issue.

Competing interests: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports.
Ethical approval: The study was approved by the local ethics committee of the hospital and each patient gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

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