Original Article

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The Relationship between Serum Vitamin D Level and the Outcome of Patients Hospitalized in the Medical Intensive Care Unit

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ABSTRACT

BACKGROUND AND OBJECTIVE: Vitamin D plays a key role in bone mineralization, muscular strength, immune system function, cardiovascular function and the health and function of brain. Since the critically ill patients hospitalized in the medical intensive care unit suffer from vitamin D deficiency due to several reasons, the present study aims to evaluate the serum vitamin D level and its association with the outcome of patients hospitalized in the medical intensive care unit.

METHODS: This cross-sectional study was conducted among all patients hospitalized in the medical intensive care unit of Ayatollah Rouhani Hospital during 16 months. Vitamin D level, age, sex, cause of admission, the glasgow coma scale (GCS) and mortality were recorded. The intensity of patients' illness was measured based on the APACHE score. The level and intensity of vitamin D deficiency were measured and compared between survivors and patients who died.

RESULTS: Of the 117 patients who entered the study, 49.6% were male. The mean age of the patients was 67.22±17.27 years. The mean glasgow coma scale was 8.41±2.5. 72.6% of the patients suffered from vitamin D deficiency (<20 ng/ml). 56 patients (47.9%) died. Vitamin D level was 14.16±12.21 in patients who died and was 21.90±18.20 in patients who survived. No significant relationship was found between mortality and vitamin D level.

CONCLUSION: Results of the present study demonstrated that mortality rate in patients with vitamin D deficiency is higher than other patients.

KEY WORDS: *Vitamin D, Mortality, Medical Intensive Care Unit, Length of stay.*

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Introduction

Vitamin D is a fat-soluble vitamin that plays a role in the regulation of calcium. The 25 (OH) vitamin D is the main storage form.

The level of vitamin D in blood depends on ultraviolet radiation onto the skin and consuming adequate food and dietary supplements (1). There are two forms of vitamin D: cholecalciferol or vitamin D3 and ergocalciferol or vitamin D2. Cholecalciferol in the skin is formed by UVB radiation (2-7). Serum 25 (OH) D level is a reliable criteria to assess serum vitamin D status (2,3,8,9).

Most known activities of vitamin D are related to calcium absorption in the intestine, calcium homeostasis and serum phosphorus. Vitamin D plays a key role in bone mineralization, muscular strength, immune system function, cardiovascular function and the health and function of brain (10-17). According to The American Association of Endocrine Surgeons, vitamin D deficiency occurs when serum 25(OH) D level is lower than 20 ng/ml. 21-29 ng/ml vitamin level is considered as inefficiency, while ≥30 ng/ml is considered as sufficient vitamin D level (6,7). In United States, vitamin D deficiency is observed in 36 to 57% of patients referred to general practitioners (18). In Australia, one in every three people suffer from vitamin D deficiency (19).

According to the Comprehensive Multicenter Bone Health Survey in Iran, moderate to severe vitamin D deficiency in age groups younger than 50 years, 50 to 60 years and older than 60 years were estimated to be 45.7, 47.2 and 44.2%, respectively for men and 41.2, 54.2 and 37.5%, respectively for women (20). About 50-60% of patients hospitalized in the medical intensive care unit suffer from vitamin D deficiency (21). According to a study conducted among 158 patients hospitalized in the medical intensive care unit in Isfahan, 93.5% of patients suffered from vitamin D deficiency and inefficiency (22).

The critically ill patients hospitalized in the medical intensive care unit suffer from vitamin D deficiency due to several reasons. In addition to critical illness, therapeutic interventions such as surgery, fluid therapy, extracorporeal oxygenation, cardiovascular bypass and plasma exchange may reduce vitamin D level. Moreover, because of reduced exposure to sunlight, increased immobility, increased conversion of 25 (OH) D to 1,25 (OH) 2D3, inflammation and impaired liver, parathyroid and kidney function as well as reduced resistance of organs and nutritional deficiency, patients hospitalized in the medical intensive care unit are at higher risk vitamin D axis disorders (23-27). Studies show the close relationship between APACHE II scoring system (Acute Physiology and Chronic Health Evaluation II score) and in-hospital mortality among critically ill patients. This model is calculated based on 12 physiological characteristics, age and former condition of patient (24, 25).

Considering the high prevalence of vitamin D deficiency in Iran and limited number of studies dedicated to the effect of vitamin D deficiency on the short term outcome of patients hospitalized in the medical intensive care unit (26,28), the present study was conducted to evaluate the serum vitamin D level and its association with the outcome of patients hospitalized in the medical intensive care unit of Ayatollah Rouhani Hospital in Babol.

Methods

This cross-sectional study was conducted (during 16 months) among all patients hospitalized in the medical intensive care unit of Ayatollah Rouhani Hospital in Babol who survived for 48 hours. Patients younger than 18 years old, pregnant women, patients treated with supplemental vitamin D, corticosteroids, diabetes, high blood pressure, malabsorption syndrome, chronic kidney disease and metastatic cancer were excluded from the study.

Sampling was done through Census method. 4 mL blood sample was collected from patients at the time of admission to measure vitamin D level. Serum vitamin D level was measured using Euroimmun kit (United States) through ELISA method (Enzyme-Linked Immunosorbent Assay).

Vitamin D level more than 30 ng/ml was categorized as sufficient level, 20 to 30 ng/ml was categorized as insufficient level, 10 to 20 ng/ml was categorized as deficient level and less than 10 ng/ml was categorized as undetectable level (6,7). Demographic characteristics (age, sex, and comorbidities), diagnosis at admission, clinical characteristics and biochemical parameters (including total serum calcium, phosphorus, creatinine, albumin and the level of vitamin D) and the use of mechanical ventilation were recorded. The intensity of patients' illness was measured based on the APACHE II score. Level and severity of vitamin D deficiency was compared between patients who survived and patients

who died. The statistical data were analyzed using SPSS software. The average variables were expressed using the mean and standard deviation. Variables lacking normal distribution were analyzed by Mann-Whitney method and other variables were analyzed by T-Test.

Variables in groups were analyzed using chi-square method. Pearson and Spearman test was used to study the relationship between vitamin D level and other variables and t-test and chi-square were used, while $p<0.05$ was considered significant.

Results

Overall, 117 patients hospitalized in the medical intensive care unit of Ayatollah Rouhani Hospital in Babol were included in the study. 49.6% of these patients were male. Their mean age was 67.22±17.27. Patients were categorized into 7 groups based on the cause of hospitalization, while the highest frequency (36.8%) belonged to the Neurology patients (table 1). 72.6% of patients suffered from vitamin D deficiency. Vitamin D level was 14.16±12.21 ng/ml in the mortality group and 17.96±18.40 ng/ml in the survived group. According to the results of this study, GCS is the independent variable for mortality (p=0.004). The level of calcium (p=0.021) and phosphorus (p=0.030) are the independent variables for affecting vitamin D deficiency.

The mean APACHE II score was calculated to be 19.48±7.27 in these patients and the mean predicted chance of mortality was 34.12±19.2%. 47.9% of patients of this study died in the medical intensive care unit. 49.4% of patients with vitamin D deficiency and 43.8% of patients without vitamin D deficiency died and no significant relationship was found between mortality and vitamin D deficiency (table 2).

According to the present study, use of mechanical ventilation and GCS at the time of admission was an independent variable of their mortality (table 3).

Table 1. The average variables of age, sex, 25 (OH) D, APACHE II, actual mortality, cause of hospitalization, etc. in patients hospitalized in the medical intensive care unit.

Variable	Patients(N=117) Mean±SD
Vitamin D level (ng/ml)	16.14±15.8
APACHE II score	19.48±7.22
Predicted mortality	34.12±19.2
The number of days of mechanical ventilation	16±17.48
Length of stay in intensive care unit (days)	20.2±17.11
Level of Calcium (milligrams per deciliter)	8.9±0.75
Level of Phosphorus (milligrams per deciliter)	4.04±1.6
GCS	8.41±2.5
	N(%)
Sex	58(49.6)
Actual mortality	56(47.9)
Cause of hospitalization	
Acute respiratory failure	17(14.5)
Heart disease	16(13.7)
Stroke	43(36.8)
After surgery	11(9.4)
Chronic respiratory failure	9(7.7)
Sepsis	6(5.1)
Other causes	15(12.8)
Mechanical ventilation	89(76.1)
Successful isolation from mechanical ventilation	39(43.8)

Table 2. Comparing variables of age, 25 (OH) D, APACHE II, length of stay in the intensive care unit, the number of days of using mechanical ventilation, calcium, GCS, phosphorus in patients with vitamin D deficiency and patients with sufficient vitamin D.

Variable	Vitamin D deficiency (20 ng/dl >) Mean±SD	Sufficient vitamin D (20 ng/dl≤) Mean±SD	P-value
Age (years)	66.88±15.79	67.88±15.79	0.803
APACHE II Score	17.72±5.77	20.14±7.68	0.109
The predicted mortality (%)	30.81±16.02	35.36±20.21	0.255
Length of stay in the intensive care unit (days)	23.75±23.57	18.87±14.97	0.187
The number of days of using mechanical ventilation	20.03±21.38	14.4±15.53	0.123
Level of Calcium (milligrams per deciliter)	8.47±0.77	8.08±0.71	0.021
Level of Phosphorus (milligrams per deciliter)	3.59±0.98	4.22±1.77	0.030
GCS	8.63±2.86	8.32±2.36	0.595

Table 3. Comparing variables of age, 25 (OH) D, APACHE II, length of stay in the intensive care unit, the number of days of using mechanical ventilation, calcium, GCS, phosphorus in the survived patients and patients who died.

Variable	Patients who died (N=56)	Patients who survived (N=61)	P-value
Age (years)	69.51±17.22	65.03±17.16	0.153
APACHE II Score	23.41±7.01	15.87±5.42	0.000
The predicted mortality (%)	44.55±19.19	24.54±13.42	0.000
Vitamin D level (nm/ml)	14.16±12.21	17.96±18.4	0.188
Length of stay in the intensive care unit (days)	14.16±12.21	21.9±18.2	0.283
Mechanical ventilation (Number [%])	50(89.3)	39(63.9)	0.001
The number of days of using mechanical ventilation	16.81±17.28	15.24±17.77	0.634
Level of Calcium (milligrams per deciliter)	8.13±0.76	8.24±0.73	0.648
Level of Phosphorus (milligrams per deciliter)	4.25±1.77	3.83±1.4	0.210
GCS	7.71±2.31	9.05±2.5	0.004

Discussion

Results of this study demonstrated that the prevalence of vitamin D deficiency in patients hospitalized in the medical intensive care unit is high. Vitamin D level in the survived patients was more that the patients who died. However, this difference was not significant. The use of mechanical ventilation and GCS at the time of admission to the medical intensive care unit was significantly related to mortality in this unit. Length of stay in the intensive care unit, calcium and phosphorus were independent variables in determining the mortality rate among patients hospitalized in the medical intensive care unit.

According to the study of Vosoughi et al., 93.5% of patients have insufficient vitamin D and the prevalence of vitamin D deficiency was high among patients hospitalized in the medical intensive care unit (21). According to the present study, the level of vitamin D in 72.6% of patients was lower than 20 ng/ml. However, no statistically significant relationship was observed between vitamin D deficiency and mortality, length of stay in the intensive care unit and length of ventilation. In a study by Venkatram et al. among 437 patients, the prevalence of vitamin D deficiency was calculated to be 77.8%. Vitamin D deficiency is an independent criteria in association with mortality in patients hospitalized in the medical intensive care unit, which is inconsistent with the present study. They also concluded that days of using mechanical ventilation and APACHE II Score at the time of admission are independent criteria in terms of their effectiveness on mortality. APACHE II Score at the time of admission was also an independent criteria in terms of association with mortality in the present study. However, no significant relationship was found between days of using mechanical ventilation and mortality. This may

be due to the fact that we calculated the total days of mechanical ventilation before admission to the medical intensive care unit. Moreover, Venkatram et al. did not observe a significant relationship between mortality, age and days of being hospitalized in the medical intensive care unit, calcium and phosphorus, which was consistent with the present study (1).

Azim et al. concluded that 19.6% of patients have normal vitamin D level and the mean level of vitamin D in patients who died (47.3±39.22) was more than patients who survived (39.7±29.31). However, no significant relationship was observed between mortality and vitamin D deficiency (16), which was inconsistent with the present study, though the definition of vitamin D deficiency is a little different in the two studies. In a study by McKinney et al., 38% of patients suffered from vitamin D deficiency and vitamin D was an independent criteria regarding the mortality rate (28).

The frequency of vitamin D deficiency in this study was significantly lower than results. This difference may be due to difference in location, sampling and inclusion and exclusion criteria. The mean length of stay in the medical intensive care unit in their study was 5.5±16.1 days, while it was 20.2±17.77 days in our study, because our study only included patients with more than 48 hours of stay in the medical intensive care unit. However, according to the study of McKinney et al., this inclusion criteria did not exist and vitamin D deficiency in patients who stayed in the medical intensive care unit for 3 days or more was 55.6%, which is closer to our calculations. Moreover, the fact that whether patients were treated with complementary therapy or not and what their comorbidities were, were not monitored (28).

According to the study of Arnson et al., 82.3% of patients suffered from vitamin D deficiency and the prevalence of vitamin D deficiency was higher than the present study. This difference may be related to higher mean age of patients and that the samples of the study were collected within 7 months (winter and spring) and samples were not adequately distributed in all seasons. The mortality rate within 60 days was not significantly different between the two groups of vitamin D deficiency and normal vitamin D level, which was consistent with the present study. In the study of Arnson et al., no significant relationship was observed between vitamin D deficiency and APACHE II, calcium and phosphorus. However, there is a significant relationship between vitamin D level and APACHE II, calcium and phosphorus in the present study and considering the metabolism of vitamin D, it seems that the results of the present study are more reliable (29). According a study by Aygencel et al., vitamin D level in 69% of patients was lower than 20 ng/ml and the frequency of vitamin D deficiency was very similar to our results. Mortality rate in the group with vitamin D deficiency was more than the group with sufficient vitamin D. However, vitamin D deficiency was not detected as an independent risk factor for mortality among patients (30).

According to the study of Moraes et al., the frequency of vitamin D deficiency (lower than 20 ng/ml) was very similar to our study. They concluded that if we consider 'Cutoff Point' for defining vitamin D deficiency to be 12 ≥, then the relationship between vitamin D deficiency and mortality will become significant (31). The frequency of vitamin D deficiency is high among patients hospitalized in the medical intensive care unit. Vitamin D level in the survived patients was more than those who did not survive. However, the difference was not statistically significant. It was also demonstrated that there is a significant relationship between the use of mechanical ventilation and GCS at the time of admission to the medical intensive care unit and the in-hospital mortality among patients hospitalized in this unit. Length of stay in the medical intensive care unit, calcium and phosphorus are not independent variables in determining the mortality rate among patients hospitalized in the medical intensive care unit. Considering the high prevalence of vitamin D deficiency, its measurement and modification is advised in patients hospitalized in the medical intensive care unit. Small sample size of this study is one of the limitations of the study. A randomized clinical study including two groups of treatment with vitamin D and without treatment is recommended.

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