VITAMIN D DEFICIENCY IN CRITICALLY ILL PATIENTS: A SINGLE CENTER CROSS-SECTIONAL STUDY

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ABSTRACT

Objective: To assess mangitude of vitamin D deficiency and its association with mortality in intensive care unit (ICU).

Study Design: Prospective observational study.

Place and Duration of Study: Aga Khan University, Karachi, from 2016 to 2017.

Methodology: All consecutive patients admitted to medical/surgical intensive care unit in a tertiary care hospital, age between 18 to 70 years were included. Vitamin D level was obtained on first day of admission. Demographic and biochemical variables were recorded. Vitamin D deficiency was defined as 25 (OH) D<20 ng/dL. Data was analyzed by SPSS version 21.

Results: A total of 178 patients were included during the study period; 116 (65%) were males and median age was 48 years (64-31). Median 25 (OH) D, ionized calcium and phosphate levels were 8.5 ng/dL (21.9-3.8), 4.32 ng/dL (4.6-4.1), and 3.2 ng/dL (4.2-2.2) respectively. Vitamin D deficiency was observed in 130 (73%) patients and only 27 (15.2%) had optimal level of vitamin D. Vitamin D deficient patients were comparatively younger with median age of 42.5 vs. 60 years (*p*-value=0.004). Vitamin D levels poorly correlated with ionized calcium and phosphate levels (0.026 (*p*-value=0.733) and 0.039 (*p*-value=0.601). No significant association was found between vitamin D deficiency and mortality with p-value of 0.796.

Conclusion: Majority of the patients admitted to intensive care unit were vitamin D deficient. Deficiency was more prevalent in younger patients. These findings highlight the need for consideration of vitamin D status and supplementation as it plays a vital role in different physiological processes in patients in the intensive care unit.

Keywords: Biomedical markers, Intensive care unit, Vitamin D.

INTRODUCTION

Vitamin D is an important fat-soluble vitamin with vital role in function and metabolism of various cell types. It is implicated in immune modulation, cell proliferation, inflammation, differentiation, angiogenesis, and apoptosis. In addition, role in different disorders such as malignancies, autoimmune disorders and chronic infections[1,2] and close association between a number of systemic disorders such as cardiovascular morbidities, obesity, some types of cancer, and diabetes type II have been described with vitamin D deficiency[2].

Estimations from various studies show that around 1 billion inhabitants throughout the globe are suffering from D deficiency[3,4] affecting people of all age groups; ranging from newborns to geriatric population and also includes pregnant women[5]. Similar to other countries of the world, Pakistan also suffers from this epidemic which affects more than half of its population, despite the fact that the country receives a large amount of sunshine due to its geographical position[5,6].

A large number of studies have linked vitamin D deficiency with multiple morbidities and adverse clinical outcomes such as sepsis, dysfunction in the organs, infections and even death in critically ill patients[74]. A recent pilot double blind randomized controlled trial (RCT) concluded that the administration of high-dose of vitamin D3 is safe and effective in maintaining sufficient concentration and associated with reduced duration of hospital stay[8].

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In critically ill patients, vitamin D deficiency ranges from 17% to 80% in reported literature[5-6]. Patients in the intensive care unit (ICU), especially those with longer length of stay are at higher risk of developing vitamin D deficiency due to insufficient exposure to sunlight, lack of nutrition, inflammation and organ failure including liver or kidney[1,2]. An increased requirement of vitamin D in tissues in patients with illnesses of critical nature, thereby causing an increased transformation of 25 (OH) D to the active 1,25 (OH) 2D has been described resulting in more reduction of 25 (OH) D level[7].

Various studies have shown decreased rates of mortality when vitamin D supplements were provided in combination with calcium rather than just by administering vitamin D alone. In a Cochrane systematic review it was identified that administration of vitamin D greatly reduced the rate of mortality in patients with vitamin D deficiency. The least amount of 25 (OH) D quintile was linked with an elevated rate of mortality, cardiovascular mortality, and cancer mortality[9-10].

There is paucity of local data on vitamin D deficiency in ICU patients, therefore, this study was designed to assess the vitamin D deficiency among the patients admitted to ICU in a large tertiary care center.

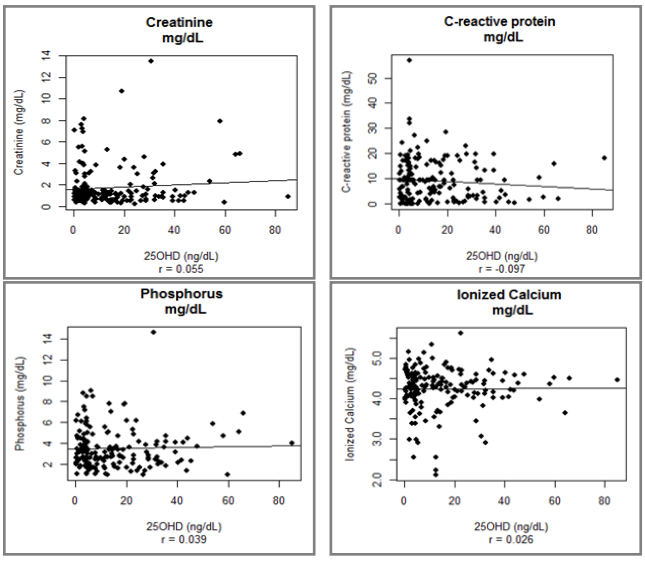
METHODOLOGY

A prospective observational study was conducted at departments of Pathology & Laboratory Medicine and Anesthesiology, Aga Khan University, Karachi Pakistan from July 2016 to July 2017. Institutional ethical review committee approval was taken for the study ((ERC ID: 3930-Pat-ERC- 15).

Patients for this study were recruited on their first day of admission to either surgical or medical ICU. Inform consent form the patient or guardian or legal care taker of the patient were taken after explaining purpose and benefits of the study and assuring confidentiality of personal information of the participants. Blood samples for biochemical analysis including creatinine, phosphorus, ionized calcium and 25 (OH) D was obtained in a gel tube from all the enrolled patient and stored at -20°C until analysis. History was obtained from medical records for 25 (OH) D analysis was obtained from all the enrolled patients, in a gel tube and stored at -20°C until analysis. Patients with 25 (OH) D level <20 ng/dL were classified as deficient and >20 ng/dL as optimal or sufficiency[21]. All the recruited patients were followed during their hospital stay for in-hospital mortality.

SPSS version 21 was used for the analysis of collected data. Continuous variables were assessed for normality of distribution using Shapiro-Wilk test and appropriate descriptive median (Q3-Q1) was calculated. Frequency and percentage was calculated for all the categorical study variables. Difference in continuous variables by 25 (OH) D level was assessed using Mann-Whitney U-Test. Pearson correlation coefficient and scatter plots were obtained to analyze the relationship of 25 (OH) D level with other laboratory indicators of the patient. Statistical significance criterion was set as two sided.

RESULTS



25OHD = 25-hydroxyvitamin D

Figure: Relationship between vitamin D level and biochemical markers.

A total of 178 patients were included in this study, with 116 (65%) male patients. The median age was calculated to be 48 years (64-31). In 20%

of patients, the primary diagnosis was neuro-surgical disease, followed by trauma (18%), acute kidney injury (14%), respiratory failure (7.8%), gastrointestinal diseases (6.7%), oncological disorders (5%), and 26.3% suffered from miscellaneous causes. All cause ICU mortality was observed in 47 (26.4%) of the study patients.

Shapiro-Wilk test for the normality of the distribution of 25 (OH) D (ng/dL), ionized calcium (mg/dL), and phosphorus (mg/dL) was rejected with *p*-value of <0.001 for each. So median (Q3-Q1) are reported Baseline characteristics of the patients are presented in table-I. Vitamin D deficiency was observed in 130 (73%) patients.

Vitamin D deficient patients were comparatively younger with median age of 42.5 vs. 60 years (*p*-value=0.004). Proportion of males among vitamin D deficient patients was relatively higher, 67.7% vs. 58.3%, however no statistically significant association of vitamin D deficiency was observed with gender (*p*-value=0.245).

Significant difference was also not noted in the levels of biochemical markers or all-cause mortality. Comparative analysis of vitamin D deficient and non-deficient groups of patients is presented in table-II.

Table-I: Median Levels of Biochemical Markers along with frequency and median levels of hyper & hypo functioning states in intensive care units patients based on upper & lower cutt-off (n=178).

Variables	Median (Q3-Q1) (n=178)	Hyper/Hypo Functioning Stats		
			Frequency (%)	Median (Q3-Q1)
25OHD ng/dL	8.5 (21.9-3.8)	Deficient <20	130 (73)	4.7 (11.7-3.2)
		Optimal ≥20	48 (27)	31.9 (41.1-24.9)
Ionized calcium mg/dL	4.32 (4.6-4.1)	Low <4.64	150 (84.3)	4.2 (4.4-4.0)
		Optimal 4.64-5.28	26 (14.6)	4.8 (4.9-4.7)
		High >5.28	2 (1.1)	-
Phosphorus Mg/dL	3.2 (4.2-2.2)	Low <2.5	54 (30.3)	2 (2.3-1.6)
		Optimal 2.5-4.5	86 (48.3)	3.3 (3.9-2.9)
		High >4.5	38 (21.3)	6 (7.2-5)

25OHD = 25-hydroxyvitamin D

Table-II: Demographic and biochemical characteristics of patients in intensive care units and distribution of subjects according to 25 (OH) D status (n=178).

Variables		Frequency (%) or Median (Q3-Q1) (n=178)	25 (OH) D Status (ng/dL)		
			<20 (n=130)	>20 (n=48)	*p*-value**
Age (Years)		48 (64-31)	42.5 (26.7-62)	60 (71.7-38.5)	0.004*
Male		65.1 (116)	67.7 (88)	58.3 (28)	0.245
Body Mass Index		26 (29-24)	26 (29-24)	28.9 (30.5-23.2)	0.151
Mortality	Expired	26.4 (47)	26.9 (35)	25 (12)	0.796
	Alive	73.6 (131)	73.1 (95)	75 (36)	
Creatinine (mg/dL)		1.1 (1.7-0.7)	1.1 (1.5-0.7)	1.15 (2.5-0.7)	0.413
C-reactive protine (mg/dL)		9.3 (16.2-2.1)	9.3 (15.4-2.5)	4.11 (13.4-1.7)	0.180
Phosphorus (mg/dL)		3.2 (4.2-2.2)	3.2 (4.3-2.3)	3.0 (4.2-2.1)	0.697
Ionized Calcium (mg/dL)		4.3 (4.5-4.0)	4.3 (4.5-4.1)	4.3 (4.5-4.1)	0.766

25OHD = 25-hydroxyvitamin D, *Statistically significant at 5% level of significance, **p-values are based on Mann-whitney U-Test for continuous variables.

Correlation between vitamin D, CRP, creatinine, ionized calcium and phosphate was assessed. No statistically significant relationship was observed between vitamin D level and biochemical markers such as creatinine, CRP, phosphorus, and ionized calcium with insignificant correlation coefficient of 0.055, -0.097, 0.039, and 0.026 respectively. Figure provides an illustration of relationship between vitamin D level and other biochemical markers of the patients.

DISCUSSION

This study was conducted with aim of assessing vitamin D status among patients admitted to ICU. Deficiency (25OHD< 20 ng/dL) was observed in majority (73%) of the patients in our study with median level of 8.5 ng/dL (21.9-3.8). Vitamin D deficiency was more prevalent at median age of 42.5 years (26.7-62) compare to patients with levels >20 ng/dL.

Vitamin D deficiency among ICU admitted patients is a global phenomena, studies from various parts of the world reported varying rates among these patients[11-15]. McKinney *et al*[16] conducted a study in a medical facility in Southeastern United States and reported 38% deficiency among ICU admitted veterans. Lucidarme *et al*[17] reported 79% deficiency among the ICU patients in France. Moromizato *et al*[12] reported 25 OHD of ≤15 ng/mL in 17% of the patients treated in medical and surgical ICUs of two teaching hospitals in Boston. A prospective cohort study by Quraishi *et al*[13] reported vitamin D deficiency in 63% of the patients admitted to a surgical ICU of a hospital in Boston. A single center observational study at a tertiary care hospital in Austria, by Amrein *et al*[14], observed 25 OHD <20 ng/ml in 60.2% of the nonsurgical and surgical critically ill patients. Study conducted in Istanbul, Turkey, by Atalan *et al*[23], reported 77.1% patients with vitamin D level <25 ng/dL. Azim *et al*[24] conducted a study in North India, including both surgical and medical cases admitted to ICU, and found deficiency in 80.4% of the patients[18-20].

Reported frequency of 73% vitamin D deficiency in our study is within the range of reported frequencies in past studies from various parts of the world. Optimal level of vitamin D in only 27% of the study sample in our setting is of concern. However, outcome based studies need to be performed for determining the beneficial effects of vitamin D supplementation. Targeted initiatives are needed in this regards[21-24]. Vitamin D supplementation in deficient patients is reported to be safe and inexpensive, as concluded by Christopher *et al*[1], considering the socio-demographic differences of our population interventional studies are warranted to establish the relationship, in the first place, and then benefits, safety and efficacy of vitamin D supplementations in these patients.

Present study has certain limitations such as small sample size and single center based study. These findings highlight the need for interventional studies to determine if supplementation with vitamin D has any role in different physiological processes in patients in the ICU.

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CONCLUSION

In this study we found that majority of the patients admitted to either medical or surgical ICU were vitamin D deficit. There was no significant association of vitamin D deficiency with other markers and mortality.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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