Original Article

Vitamin D deficiency is associated with increased mortality in critically ill patients especially in those requiring ventilatory support

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ABSTRACT

Introduction: Vitamin D (VitD) classically recognized for its role in the musculoskeletal system, has been implicated in myriad of conditions such as diabetes, immune dysfunction, cancers, heart disease, metabolic syndrome, etc. We studied the role of VitD in acute care setting and its correlation with mortality. **Materials and Methods:** A total of 85 consecutive consenting patients admitted in medical intensive care unit of tertiary care hospital who fulfilled the inclusion criteria were included. All patients were evaluated clinically, and blood samples were collected for hemogram, biochemical investigations including serum calcium, phosphorus, alkaline phosphatase, magnesium, along with 25(OH) VitD, 1,25(OH) VitD and intact parathormone levels. Simplified acute physiology score (SAPS II) was calculated for all patients. **Results:** VitD was deficient (<30 ng/ml) in 27 patients (32%). The overall mortality was more in VitD deficient group as compared to VitD sufficient group (74 vs. 41%; $P < 0.05$). The actual mortality in VitD deficient group was higher than the mortality predicted by SAPS II score (50 vs. 74%; $P < 0.0507$). VitD deficiency was also associated with more mortality among those requiring ventilator support (95% vs. 40%; $P < 0.05$) as well as with higher blood glucose (124.5 ± 29.7 vs. 94.8 ± 19.8: $P < 0.01$) levels. **Conclusion:** VitD deficiency was associated with increased mortality, poor ventilator outcomes, and increased blood glucose in critically ill patients.

Key words: Blood glucose, mortality, vitamin D

Introduction

Vitamin D (VitD) is associated with both classical (actions on the musculoskeletal system) and non-classical actions (which are related to the role in the immune system, cell growth and differentiation and regulation of hormone secretion).[1] The role of VitD and impact of VitD deficiency has been widely studied in chronic conditions like cardiovascular disorders, diabetes mellitus, polycystic ovaries, autoimmune disorders, etc.[1,2] All-cause mortality has been foun0d to be more with VitD deficiency. Furthermore, VitD supplementation has been shown to reduce overall mortality.[3,4] However, data is significantly lacking in critically ill patients in acute care setting. A limited number of studies have previously dealt with the subject, which had shown increased mortality, increased infections and more likelihood of renal impairment. No study from India until date deals with the topic to the best of our knowledge. The aim of the current study was to study the impact of VitD deficiency on outcomes in critically ill patients.[5-7]

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Materials and Methods

The study was conducted at a large tertiary care center hospital run by the Municipal Corporation in Mumbai, India (latitude 18°55'N longitude 72°54'E). After Institutional Ethics committee approval consecutive consenting patients (consent of legally accepted representative in case of patients

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who cannot give valid consent) admitted to the critical care unit of the Institute were included in the study excluding those with tuberculosis, chronic kidney disease, chronic liver disease, acute coronary syndromes, known malignancy, known diabetes mellitus, immediate post-operative (surgery within last 14 days), pregnancy (currently pregnant or pregnancy in last 2 years) and those on anti-epileptic medications or corticosteroids prior to sample collection. Simplified acute physiology score II (SAPS II) and predicted mortality rate (PMR) calculated at 24 h of admission to intensive care unit from age, heart rate, systolic blood pressure, temperature, need for mechanical ventilation, arterial oxygen partial pressure (by arterial blood gas analysis), fraction of inspired oxygen, urine output, blood urea nitrogen, white blood cell count, sodium, potassium, bicarbonate, bilirubin, Glasgow coma scale and presence of chronic diseases. Samples for analytes mentioned were collected at the time of admission to the critical care unit. Indicated samples were repeated as directed by the intensive care unit team protocol as per case to case basis. Worst value within the first 24 h was used for calculation of the score.[8] An additional fasting blood glucose sample was collected if the initial sample collection was a non-fasting.

Calcium metabolism parameters (serum calcium, magnesium, phosphorus, albumin, alkaline phosphatase, serum creatinine, 25(OH) VitD3 [radioimmunoassay, by biosource [analytical sensitivity; AS-0.5 ng/ml] and intact parathyroid hormone [PTH]] by immunoradiometric assay by Immunotech; AS <0.2 pg/ml) were assayed from the blood sample collected within 3 h of admission to intensive care unit. VitD deficiency was defined as level below 20 ng/ml, insufficiency as level between 20 and 30 ng/ml and sufficiency as level above 30 ng/ml.[9]

Statistical analysis was performed by SPSS version 19 manufactured by IBM, Armonk, Newyork, US. Mean ± standard deviation (standard error of mean or quartiles wherever applicable) were given as descriptive statistics. Log transformations were applied to highly skewed variables. Chi-square test of independence or Fisher's exact test was used to test the distribution of discrete variables. The Mann-Whitney rank sum test was used to test the difference among groups in continuous variables at baseline. $P < 0.05$ was considered as significant. A linear regression analysis was done to assess the individual effect of various parameters on mortality.

Results

Out of the 85 patients included 64 (75%) were males and 21 (25%) were females. The mean age was 42.4 ± 16.9 years (range 19-75 years). 16 (19%) of cases had some other chronic medical illness apart from acute medical condition (12 were known hypertensive, two had chronic obstructive airway disease one had a past history of ischemic heart disease and 1 had cardiomyopathy). 73 (86%) had acute infection. 44 of the included patients died (actual mortality 52%). Mean VitD was 41.5 ± 24 ng/ml (range 4.8-142.1 ng/ml). 27 (32%) cases had VitD deficiency/insufficiency, while remaining 58 (68%) were VitD sufficient. The average SAPS II score was 48 (Q1 = 31; Q3 = 64) and PMR was 47 ± 30.61 (range 4.2-98.5). The actual observed mortality was 44/85 (52%). There was no difference in age, sex distribution and corrected calcium levels amongst the VitD deficient/insufficient and sufficient groups. The PTH levels were higher and 1.25 VitD levels lower in VitD deficient/insufficient group; however, the differences did not reach statistical significance. In our study, we found higher blood glucose levels in VitD deficient/insufficient cases as compared VitD sufficient group (124.5 ± 29.7 vs. 94.8 ± 19.8; $P < 0.01$). SAPS score in VitD deficient/insufficient group was 53 (Q1 = 32; Q3 = 62), where as in VitD sufficient group it was 46 (Q1 = 30; Q3 = 66) ($P = 0.47$). The differences in parameters mentioned among two groups are summarized in Table 1. The PMR was 50% in VitD deficient/insufficient group whereas it was 44% in VitD sufficient group ($P = 0.43$). The actual mortality was 20/27 (74%) in VitD deficient/insufficient group and 24/58 (41%) in VitD sufficient group. The difference in actual mortality was significant ($P = 0.004$). The difference between predicted and actual mortality neared, but did not reach statistical significance in VitD deficient/insufficient group ($P = 0.0507$). Thus, VitD deficiency/insufficiency was associated with higher mortality when compared to VitD sufficient population. The mortality was more

Table 1: Comparison of vitamin D deficient/insufficient and vitamin D sufficient groups

	25 (OH) vitamin D deficient/ insufficient group	25 (OH) vitamin D sufficient group	*P* value
Age (years)	42±18	43±17	0.804
Sex (male/female)	20/7	44/14	
Blood sugar (mg %)	124.5±29.7	94.8±19.8	0.001
Calcium (mg %) (8.5-11)	8.11±1.46	8.12±1.29	0.97
Phosphorus (mg %) (2.5-5.5)	3.55±1.04	4.05±1.07	0.03
PTH (pg/ml) (14-72)	59.3 (Q1=37; Q3=97)	52.4 (Q1=24.6; Q3=136.9)	0.31
1,25(OH) vitamin D3 (pg/ml) (15-50)	21.92±19.49	32.98±25.50	0.052
SAPS	53 (Q1=32; Q3=62)	46 (Q1=30; Q3=66)	0.4710

25 (OH): 25-hydroxyvitamin D, PTH: Parathyroid hormone, SAPS: Simplified acute physiology score

than what was predicted by SAPS II score in VitD deficient/insufficient groups. There was no difference in mortality in VitD deficient (9/12 died; mortality 75%) and VitD insufficient (11/15 died; mortality 73.4%) groups ($P = 0.73$). The difference in predicted and actual mortality is shown in Figure 1. There was no difference in number of patients with VitD deficiency/insufficiency (21/27) and sufficiency (40/54) who required ventilator support during the critical care unit stay, but the mortality rate among patients requiring ventilator support was more in VitD deficient/insufficient (20/21 died) group when compared to VitD sufficient (16/40 died) group($P = 0.0001$). The number of patients requiring ventilator support and mortality rates among them is shown in Figure 2.

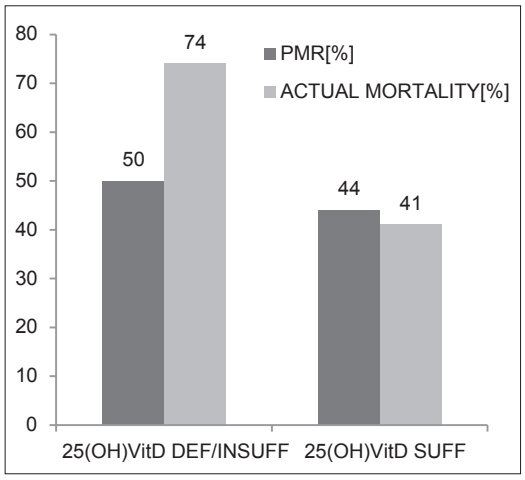

Figure 1: Comparison of predicted and actual mortality (expressed as percentage) Amongst 25(OH) vitamin D (VitD) deficient/insufficient versus sufficient groups. There was no difference in predicted mortality by simplified acute physiology score II score among the 2 groups ($P = 0.43$), but the actual mortality was much more than predicted mortality in 25(OH) VitD deficient/insufficient groups. The difference in actual mortality was significant ($P = 0.004$). PMR=Predicted mortality rate

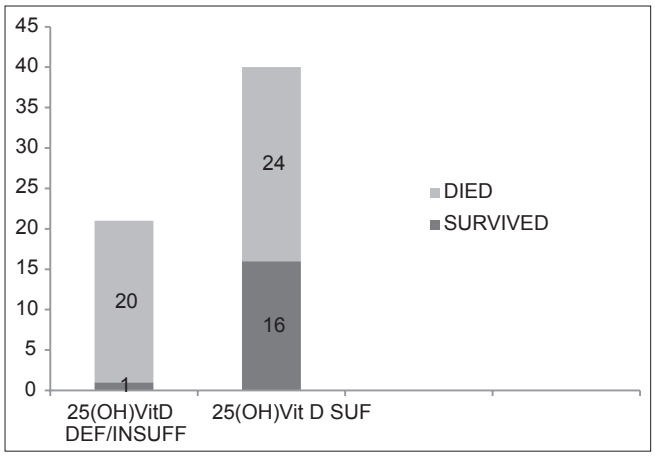

Figure 2: Outcomes of patients requiring ventilator support amongst vitamin D (VitD) deficient/insufficient and VitD sufficient groups ($P = 0.0001$)

Logistic regression showed that VitD deficiency/insufficiency was significantly associated with mortality with and odds ratio of 4.125 (confidence interval =1.56:11.06).

VitD deficiency was the second strongest factor correlated with mortality after SAPS score. The result of logistic regression and mortality risk associated is shown in Table 2.

Discussion

VitD is classically known for its actions on the musculoskeletal system. However, more and more focus is being shifted on non-classical actions of VitD, which include hormone secretion, cell cycle regulation and immunomodulation.[1] VitD deficiency has been independently proven to increase the risk of all-cause mortality in the general population.[3,4] However data is scanty regards its role in acute care setting. The study focuses on the role of VitD in acute care setting and tries to understand the impact of VitD deficiency in critically ill patients. This is the first study in Indian subcontinent trying to focus on the role of VitD in acute care setting to the best of our knowledge.

We found the prevalence of VitD deficiency to be 27% which is similar to reports from previous studies (around 20-40%), though some authorities have reported higher prevalence. Shivane *et al.* in their study among healthy volunteers in western India found much higher prevalence of VitD deficiency (76%).[5,6,10,11]

Previous studies have looked at VitD deficiency/insufficiency and mortality in critically ill patients. Paul lee first reported increased mortality among VitD deficient/insufficient groups and stated that VitD deficiency was the second most important association with mortality after SAPS score.[12]

Table 2: Logistic regression analysis for mortality risk using possible responsible variables

	P value	Odds ratio	95% confidence interval
Age	0.10	1.07	0.98-1.16
Male sex	0.06	0.02	0.01-1.31
Presence of underlying chronic medical illness	0.14	6.97	0.50-96.16
Duration of illness symptoms prior to shifting to intensive care	0.4	1.09	0.88-1.37
Mean arterial blood pressure	0.54	0.98	0.92-1.04
Glasgow coma scale	0.08	0.43	0.17-1.12
Creatinine	0.83	0.84	0.14-3.15
Albumin	0.53	1.76	0.29-1.79
Blood sugar	0.60	1.04	0.96-1.06
SAPS II score	0.001	1.25	1.09-1.43
Cortisol	0.61	1.02	0.93-1.11
Vitamin D deficiency	0.04	4.12	1.56-11.06

SAPS: Simplified acute physiology score II

Our study agrees with these observations. A retrospective study by Venkatram *et al.* have reported prevalence of VitD deficiency to be 77.8% in medical intensive care unit. Patients with VitD deficiency were younger and there was more prevalence of renal impairment. Hospital mortality was higher amongst VitD deficient patients ($P < 0.001$), but there was no difference in hospital stay and ventilator days.[5]

The present study also found increased mortality in VitD deficiency/insufficiency, but the ventilator outcomes were extremely poor in VitD deficiency/insufficiency group, though there was no significant difference in ventilator requirement in two groups. Respiratory muscle weakness attributable to VitD deficiency may result in poor ventalitory outcomes in VitD deficient group.[13]

Previous studies in hospitalized patients have correlated VitD deficiency with renal impairment, more severity of illness, more blood culture positive infections (odds ratio = 1.64) and mortality among critically ill (odds ratio = 1.69).[6,7,14] VitD has also been attributed in sepsis as it influences local immune responses and systemic inflammatory process as suggested by Kempker *et al.*[15]

VitD deficiency is associated with increases incidence of diabetes, poor glycemic control in diabetics as well as more micro and macrovascular complications of diabetes. In our study, we found higher blood glucose levels in VitD deficient/insufficient cases as compared VitD sufficient group (124.5 ± 29.7 vs. 94.8 ± 19.8; $P < 0.01$). To the best of our knowledge, no study previously has reported relation of increased blood glucose with VitD deficiency in critical care setting. VitD is important for secretion of insulin as well as VitD deficiency is associated with insulin resistance, and these could be the possible reasons for high blood glucose in VitD deficient group. The patients who were known diabetic were excluded from this subset analysis ($n = 4$; two each in deficient and sufficient groups).[16]

VitD deficiency is associated with myopathy that might also be associated with diaphragmatic and respiratory muscle weakness. The high mortality in VitD deficient/insufficient group who required ventilator support may be due to this and also due to the association of VitD deficiency/insufficiency with a wide range of pulmonary diseases including viral and bacterial respiratory infection, asthma and chronic obstructive pulmonary disease.[13]

Critical illness is associated with severe bone resorption as pointed out by Nierman *et al.* whereas Van den Berghe tried VitD supplementation in critically ill. This failed to normalize VitD levels in most and no significant decrease was recorded in bone resorption markers. However the doses used by Van den Berghe were much less (200-500 IU/day).[17,18]

Critically ill patients usually have multisystem involvement and role of VitD is being implicated in many systems beyond the musculoskeletal. There is plenty of data about VitD in chronic diseases, but there are very few studies about VitD in acute care setting. The principle of critical care is to target all reversible factors that may benefit the patient. There is no denial of the fact that primary medical illness and underlying comorbidities are going to be the most important factors affecting survival and outcome in medical intensive care. Correction of VitD deficiency/insufficiency may at least improve ventilatory outcomes, reduce stress induced hyperglycemia, reduce renal dysfunction and may protect against bone resorption in critically ill patients. More studies regarding this as well as a therapeutic intervention trials regarding same may further clarify about the role of VitD in critical care setting.

Lack of intervention and treatment of VitD deficiency can be one of the major limitation as well as future study direction from the study. A smaller sample size in the present study is not enough for the drawn conclusion and a larger sample size and involvement of multicentric trials preferably involving wider spectrum of critically ill patients can probably widen our knowledge horizon regarding the crucial role of VitD.

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