Vitamin D (25OHD2) and Calcium status in Critically Ill Elderly patients and its association with clinicodemographic profile and clinical outcome

Dr. Abhishek Shukla, Dr. Amita Shukla, Ms. Pankhuri Misra

ABSTRACT

Aim: To assess the serum vitamin D and calcium status in elderly critically ill patients and to study its correlates and clinical impact.

Method: A retrospective record review of 267 elderly (≥60 years) non-COVID ICU admissions was done. Demographic and clinical profile of the patients was noted. Vitamin D insufficiency, deficiency and severe deficiency was defined as serum vitamin D levels 20-29.9, 10-19.9 and <10 ng/ml respectively. Hypocalcemia was defined as S. calcium levels <8 mg/dl. History of daily milk intake, weekly sun exposure and vitamin D supplementation during last six months was obtained. Chi-square, ANOVA and Pearson correlation coefficient were used to analyze the data.

Results: Prevalence of vitamin D insufficiency, deficiency and severe deficiency was 18.4%, 57.3% and 24.3% respectively. Prevalence of hypocalcemia was 40.8%. Lower vitamin D levels were significantly associated with lower mean BMI, lower mean serum calcium levels and longer duration of ICU stay. There was a significant positive correlation between vitamin D levels and serum calcium levels. Failure to ensure daily intake of milk and get >2 hours weekly exposure to the Sun was significantly associated with vitamin D deficiency and severe deficiency. Intake of vitamin D supplementation during last six months had a protective effect against vitamin D deficiency and severe deficiency.

Conclusion: Vitamin D insufficiency and deficiency was widespread in elderly critically ill patients and was correlated with serum calcium levels.

Key words: Critically ill, Elderly patients, hypocalcemia, vitamin D deficiency, ICU outcome.

INTRODUCTION

Vitamnin D is the major hormone involved in mineral ion, especially calcium homeostasis regulation[1,2]. It is unique in that it can, not only be ingested in the diet as cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2) but can also be synthesized in the skin when sunlight exposure is adequate. Despite dual mechanisms of attainment, vitamin D deficiency is not uncommon in many countries throughout the world and can lead to disease. Paradoxically, despite abundance of sun exposure, the prevalence of vitamin D deficiency in healthy Indian population is reported to be as high as 70-100%[3]. Deficiency of vitamin D is probably the most widely spread yet one of the most ignored nutritional deficiencies throughout the world[4]. Elderly population is at a higher risk of vitamin D deficiency owing to a fall in dietary intake of vitamin D coupled with a reduction in cutaneous synthesis[5]. Majority of elderly persons have vitamin D deficiency[6]. Vitamin D deficiency in elderly places them at an increased risk of fall in calcium levels which has a direct impact on the bone health[6,7]. Apart from the direct impact on bone health, vitamin D also predisposes the elderly to illnesses like sepsis, cardiovascular and metabolic disorders as well as cancer[5,8]. Previous evidence has shown that vitamin D deficiency prevalence is higher in critically ill patients as compared to that in general population[9,10]. There are some studies reporting an association between vitamin D status and ICU outcomes in critically ill adult and child patients[11-13], however, not much has been reported with respect to elderly population. Our facility is a specialized geriatric care centre that also provides ICU services to critically ill elderly, hence we made an attempt to evaluate vitamin D deficiency status in critically ill elderly patients and to correlate it with serum calcium levels and ICU outcomes.

MATERIAL AND METHOD

This study was a retrospective record review of 267 elderly (aged ≥60 years) non-COVID ICU admissions at a specialized geriatric care facility over a period of one year. Being retrospective in nature, waiver of informed consent and permission for use of data was obtained from the appropriate institutional authority.

Details such as age and sex were noted. Presence of comorbidities such as diabetes, hypertension, cardiovascular disease, renal disease, respiratory illness, liver and other gastrointestinal diseases, and neurological diseases was noted. Total number of comorbid conditions was calculated.

At admission serum vitamin D (Serum 25(OH)D_2) and calcium levels were noted. The following criteria was used to depict vitamin D status:

≥30 ng/ml	-	Normal
20-29.9 ng/ml	-	Vitamin D insufficiency
10-19.9 ng/ml	-	Vitamin D deficiency
<10 ng/ml	-	Severe vitamin D deficiency

Serum calcium level <8 mg/dl was labelled as hypocalcemia.

Dietary milk intake, weekly sun exposure and history of vitamin D supplementation during the last six months was enquired and noted.

Duration of ICU stay was noted. Outcome was noted in terms of mortality.

Data was analyzed using IBM Stats 25.0 software. Independent samples' 't'-test, chi-square and Fisher exact tests were used for comparison of data.

RESULTS

Age of patients ranged from 60 to 93 years. None of the elderly had serum 25(OH)D_2 levels in normal range (≥30 ng/ml). Prevalence of vitamin D deficiency was 81.6%. Majority of patients (n=153; 57.3%) had vitamin D deficiency followed by those having severe vitamin D deficiency (n=65; 24.3%). Remaining 49 (18.4%) had vitamin D insufficiency. No significant association of vitamin D levels was observed with age and sex. Mean body mass index of patients showed a significant decreasing trend with decreasing serum vitamin D levels (p=0.007). No significant association of vitamin D levels was observed with independent comorbid conditions as well as total number of comorbid conditions (p>0.05). However, serum calcium levels showed a significant declining trend with decreasing vitamin D levels (p<0.001). Duration of ICU stay ranged from 1 to 45 days and was significantly lower in those with vitamin D deficiency (7.85±4.60 days) as compared to those having vitamin D insufficiency (9.88±5.50 days) and those having severe vitamin D deficiency (9.25±7.08 days). There were 10 (3.7%) mortalities. The mortality rate in vitamin D insufficiency, deficiency and very severe deficiency groups was 4.1%, 3.3% and 4.6% respectively, thus showing no significant difference among groups (p=0.833) (Table 1; Fig. 1).

A significant association was found between daily intake of milk and vitamin D status (p=0.003). More than 2 hours/week exposure to the sun showed a declining trend with declining vitamin D levels, statistically it was borderline non-significant (p=0.052). Increased frequency of vitamin D supplement intake during last 6 months was associated with relatively higher vitamin D status (p=0.004). Prevalence of hypocalcemia was 12.2%, 35.9% and 73.8% respectively in vitamin D insufficient,

deficient and very severely deficient groups ($p<0.001$). There was a positive significant correlation between serum $25(OH)_2$ Vitamin D and serum calcium levels ($r=0.323$; $p<0.001$) (Table 2; Fig. 2).

DISCUSSION

In the present study, none of the elderly critically ill patients had vitamin D levels in normal range. Insufficiency, deficiency and severe deficiency of $25(OH)_2$ Vitamin D levels was observed in 18.4%, 57.3% and 24.3% of the patients. Vitamin D deficiency has been reported to be highly prevalent in critically ill patients. Amrein *et al.*[14] in their study found only 13.6% of their critically ill patients with normal vitamin D levels. In their study vitamin D insufficiency and deficiency was seen in 26.3% and 60.2% patients respectively. In a recent study, Xie *et al.*[15] found that 72.41% of critically ill patients in their study had vitamin D levels <30 ng/ml. Interestingly, all these studies were conducted in adult patients as compared to critically ill geriatric patients in the present study. A higher prevalence of vitamin D deficiency and that of patients with severe deficiency in the present study could be attributed to relatively higher age of the patients in the present study. Age seems to have an effect on vitamin D levels as the vitamin D deficiency in paediatric critically ill patients has been reported to be much lower than that in the adults. In their study, Rippel *et al.*[16] found only 34.5% of critically ill children to be vitamin D deficient which is much below than that seen in studies conducted among adults as highlighted above. It, thus seems, that with increasing age, the probability of vitamin D deficiency seems to increase. The findings of the study in fact show that vitamin D deficiency is more a rule than an exception in critically ill elderly patients.

In the present study, we observed a significant association of vitamin D levels with body mass index and serum calcium levels. However, we did not find a significant association of comorbid conditions with vitamin D levels. We also did not find a

significant association of number of comorbid conditions with vitamin D status. A non-linear relationship between vitamin D status and duration of ICU stay was observed, however, no such significant relationship between mortality and vitamin D status was observed.

The relationship between calcium and vitamin D levels in elderly as seen in the present study is in consonance with the observation of Rippel *et al.*[16] in paediatric population. In fact, similar to the present study, they also failed to find a significant association between vitamin D levels and clinical outcome of the ICU patients. Contrary to the findings of the present study, a number of meta-analyses show a significant association of vitamin D deficiency with ICU outcomes like duration of stay and mortality[11-13]. The findings of the present study are in agreement with the observation of Xie *et al.*[15] who also found that despite high prevalence of vitamin D deficiency in critically ill patients, it did not emerge as an independent predictor of hospital mortality. The absence of such relationship in the present study could be owing to a much lower overall ICU mortality rate in the present study. In other studies that also reported a low ICU mortality rate, there was no significant association between vitamin D status and mortality[9].

Another reason for absence of association between vitamin D deficiency and ICU outcomes in the present study could be owing to the physiological reasons behind such deficiency. In the present study, vitamin D deficiency emerged as an effect of nutritional deficiency governed by lower amount of sun exposure and lesser intake of milk as well as lower serum calcium levels, whereas a number of studies have found it to be a physiological outcome during the clinical course in ICU patients. Amrein *et al.*[17]

in their study reported it as a result of dysregulated vitamin D metabolism leading to rapid fall in vitamin D levels after ICU admission. A similar opinion was made by Lee *et al.*[18] too. Contrary to these studies, the present study recorded vitamin D status at the time of admission itself. Thus, studies showing a relationship of vitamin D levels with clinical outcome might have recorded it as a poor clinical course itself instead of a prognostic factor. Further studies to explore this relationship are warranted.

The present study is first report evaluating the vitamin D status in geriatric critically ill patients and has revealed some interesting relationships. Being a retrospective study, the data collection could not be structured effectively. In most of the previous studies, the outcomes have been extended beyond ICU discharge too and have been able to find some significant associations. Further studies on a larger sample size, using a prospective study design and longer duration of follow-up are recommended.

CONCLUSION

Prevalence of vitamin D deficiency in critically ill geriatric patients was 81.6%. Nearly one-quarter of patients had severe deficiency. However, despite this high prevalence of vitamin D deficiency, they did not seem to affect the clinical outcomes. Vitamin D deficiency and its severity showed a significant association with dietary intake of milk, lower serum calcium levels and lesser exposure to the sun. Further studies on a larger sample size with longer duration of survival outcomes are recommended to understand this relationship further.

REFERENCES

1 Holick MF. High Prevalence of Vitamin D Inadequacy and Implications for Health. Mayo Clin Proc. 2006;81(3):353-73.

2 Holick MF, Krane SM. Bone and Mineral Metabolism in Health and Disease. In: Braunwald F, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL et al. Harrison's Principles of Internal Medicine: 17th ed. New York, NY: Mcgraw Hill; 2008. P.2365-76.

3 Ritu G, Gupta A. Vitamin D Deficiency in India: Prevalence, Causalities and Interventions. Nutrients. 2014;6(2):729-775.

4 Van Schoor NM, Lips P. Worldwide Vitamin D Status. Best Pract. Res. Clin. Endocrinol. Metab. 2011;25:671–680.

5 Meehan M, Penckofer S. The Role of Vitamin D in the Aging Adult. J Aging Gerontol. 2014 Dec;2(2):60-71.

6 Bischoff-Ferrari HA. Vitamin D beim geriatrischen Patienten [Vitamin D in geriatric patients]. Internist (Berl). 2020 Jun;61(6):535-540.

7 Veldurthy V, Wei R, Oz L, Dhawan P, Jeon YH, Christakos S. Vitamin D, calcium homeostasis and aging. Bone Res. 2016 Oct 18;4:16041.

8 Boucher BJ. The problems of vitamin d insufficiency in older people. Aging Dis. 2012 Aug;3(4):313-29.

9 Chen KW, Chen CW, Yuan KC, Wang IT, Hung FM, Wang AY, *et al.* Prevalence of Vitamin D Deficiency and Associated Factors in Critically Ill

Patients: A Multicenter Observational Study. Front Nutr. 2021 Dec 13;8:768804.

10. Zajic P, Amrein K. Vitamin D deficiency in the ICU: a systematic review. Minerva Endocrinol. 2014 Dec;39(4):275-87.

11. Zhang YP, Wan YD, Sun TW, Kan QC, Wang LX. Association between vitamin D deficiency and mortality in critically ill adult patients: a meta-analysis of cohort studies. Critical Care 2014; 18: 684.

12. de Haan K, Groeneveld AB, de Geus HR, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Crit Care. 2014 Dec 5;18(6):660.

13. McNally JD, Nama N, O'Hearn K, Sampson M, Amrein K, Iliriani K, McIntyre L, Fergusson D, Menon K. Vitamin D deficiency in critically ill children: a systematic review and meta-analysis. Crit Care. 2017 Nov 23;21(1):287.

14. Amrein K, Zajic P, Schnedl C, Waltensdorfer A, Fruhwald S, Holl A, Purkart T, Wünsch G, Valentin T, Grisold A, Stojakovic T, Amrein S, Pieber TR, Dobnig H. Vitamin D status and its association with season, hospital and sepsis mortality in critical illness. Crit Care. 2014 Mar 24;18(2):R47.

15. Xie J, Chen Q, He D. Abnormal blood 25-hydroxyvitamin D in critically ill patients: prevalence, predictors, and its association with in-hospital mortality. Eur J Med Res. 2022 Jul 6;27(1):111.

16. Rippel C, South M, Butt WW, Shekerdemian LS. Vitamin D status in critically ill children. Intensive Care Med. 2012 Dec;38(12):2055-62.

17. Amrein K, Christopher KB, McNally JD. Understanding vitamin D deficiency in intensive care patients. Intensive Care Medicine 2015. 41 1961–1964.

18. Lee P. Vitamin D metabolism and deficiency in critical illness. Best Practice and Research: Clinical Endocrinology and Metabolism 2011. 25 769–781.

Table 1: Comparison of Demographic and Clinical Profile between Critically ill Elderly patients with and without Hyponatremia

SN	Characteristic	Insufficiency (20-30 ng/ml) (n=49)	Deficiency (10-19.9 ng/ml) (n=153)	Severe deficiency (<10 ng/ml) (n=65)	Statistical significance 'p'-value
1.	Mean age±SD (Range) years	71.35±7.74 (60-90)	73.08±7.67 (60-93)	72.63±8.23 (60-89)	0.403
2.	Male:Female	30 (61.2%): 19 (38.8%)	90 (58.8%): 63 (41.2%)	30 (46.2%): 35 (53.8%)	0.166
3.	Mean BMI±SD (kg/m^2)	21.04±2.80	20.66±2.84	19.40±3.63	0.007
4.	Comorbid conditions				
	Diabetes	19 (38.8%)	63 (41.2%)	24 (36.9%)	0.833
	Hypertension	24 (49.0%)	82 (53.6%)	30 (46.2%)	0.576
	Cardiovascular disease	15 (30.6%)	45 (29.4%)	16 (24.6%)	0.722
	Renal disease	20 (40.8%)	50 (32.7%)	26 (40.0%)	0.432
	Resp. illness	11 (22.4%)	35 (22.9%)	15 (21.5%)	0.977
	Liver Disease	11 (22.4%)	24 (15.7%)	7 (10.8%)	0.237
	Other gastrointestinal diseases	5 (10.2%)	22 (14.4%)	7 (10.8%)	0.644
	Neurological illness	12 (24.5%)	42 (27.5%)	14 (21.5%)	0.647
5.	Mean No. of comorbidities±SD	2.41±1.12	2.37±1.19	2.14±1.14	0.351
6.	Mean S. Calcium±SD (mg/dl)	11.79±2.78	9.70±4.07	7.25±1.28	<0.001
7.	Mean duration of ICU stay±SD (Range) days	9.88±5.50 (2-32)	7.85±4.60 (1-36)	9.25±7.08 (2-45)	0.041
8.	Mortality	2 (4.1%)	5 (3.3%)	3 (4.6%)	0.883

Table 2: Determinants of Vitamin D deficiency and association with hypocalcemia in elderly critically ill patients

SN	Characteristic	Insufficiency (20-30 ng/ml) (n=49)		Deficiency (10-19.9 ng/ml) (n=153)		Severe deficiency (<10 ng/ml) (n=65)		Statistical significance 'p'-value
		No.	%	No.	%	No.	%	
1.	Daily intake of milk	29	59.2	66	43.1	18	27.7	0.003
2.	>2 hr weekly exposure to sun	13	26.5	27	17.6	6	9.2	0.052
3.	Vitamin D supplement intake during last 6 months	11	22.4	11	7.2	4	6.2	0.004
4.	Hypocalcemia (S. Ca^{++} < 8 mg/dl	6	12.2	55	35.9	48	73.8	<0.001

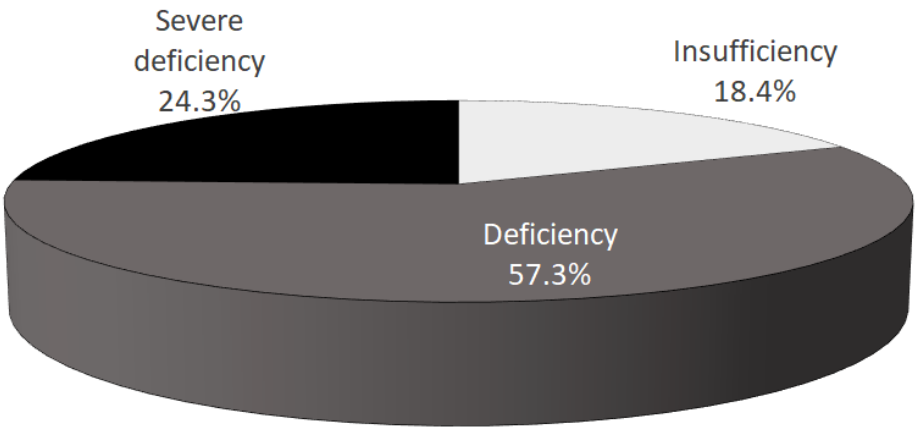

Fig. 1: Distribution of cases according to vitamin D status

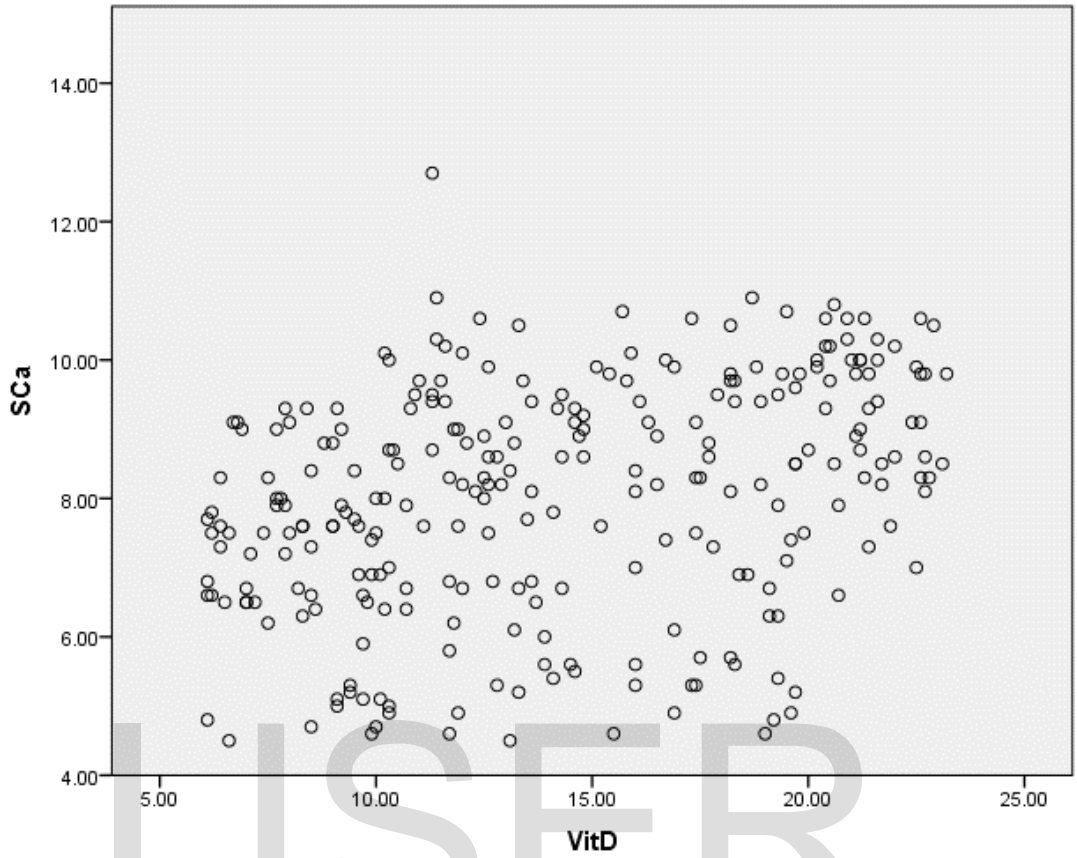

Fig. 2: Correlation between Serum Vitamin D and Calcium levels in elderly critically ill patients (r=0.323; p<0.001)