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Review

A Review of Vitamin D Deficiency in the Critical Care Population

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Abstract: It is well documented that a large percentage of the general population is either vitamin D insufficient or deficient. Vitamin D deficiency adversely affects bone health. More recently, it has been reported that vitamin D is an important component in immune function and glycemic control Substantial data exist that demonstrate an association between vitamin D insufficiency/deficiency and mortality/clinical outcomes of critically ill patients. The larger clinical trials addressing this association have demonstrated an increased odds ratio for mortality in both vitamin D insufficient and deficient patients when compared to those with sufficient vitamin D. There is also some evidence that vitamin D status worsens during critical illness without supplementation of this vitamin. Supplementation of vitamin D during critical illness of patients with vitamin D deficiency has been studied, but not in great detail. Daily supplementation of the recommended dietary allowance (RDA) of vitamin D does very little to improve the 25(OH)D serum concentrations in the critically ill patients with vitamin D insufficiency or deficiency. There is some evidence that high-dose therapy of vitamin D improves the depressed serum concentrations of this vitamin; however, there are no clinical outcome data available yet. The association between vitamin D insufficiency or deficiency and clinical outcome in the critically ill appears to be important. Supplementation of vitamin D will increase the serum concentrations of this vitamin; however the optimal dose needs to be identified along with an assessment of clinical outcome.

Key words: vitamin D; critical illness; ergocalciferol; cholecalciferol

1. Introduction

Vitamin D is a required nutrient in the human diet. The Food and Nutrition Board Recommended Dietary Allowance (RDA) for vitamin D in the first year of life is 400 IU daily. From 1 to 70 years of age the daily RDA is 600 IU and it increases to 800 IU for those adults over 70 [1]. It is recognized that vitamin D is important in bone health and it is critical in calcium and phosphorus balance. Vitamin D deficiency is a frequently reported medical problem as studies are reporting wide spread prevalence in all populations. As many as 1 billion people on earth are estimated to have some degree of vitamin D deficiency [2,3]. Populations at risk for vitamin D deficiency include breast fed infants, individuals living at high altitudes because of limited UV light exposure, and individuals with dark skin. Other groups at risk for vitamin D deficiency include individuals with high body mass index (BMI) because of supposed sequestration of dietary vitamin D in adipose tissue and patients with chronic kidney disease [1]. Supplementation is available as oral vitamin D_2 and D_3; however, there continues to be controversy over whether the D3 product is the superior one of the two. Gastrointestinal catabolism via cytochrome P-450 3A4 is much higher for vitamin D2 compared to vitamin D3. This could limit the pharmacological effects of this form of vitamin D. Currently a parenteral preparation of Vitamin D as a single-entity product is not available in the United States.

Vitamin D deficiency is known to cause rickets in children and increases the risk for osteoporosis in adults [1]. Recent literature has shown that vitamin D has more functions than regulating calcium and phosphorus homeostasis [4–12]. A summary of vitamin D functions and biologic effects is depicted in Table 1. This table highlights the importance of adequate vitamin D intake in all populations. It is also notable that vitamin D up regulates and down regulates >2000 genes [13]. Generally, vitamin D status is defined by using the serum concentration of 25-hydroxyvitamin D [25(OH)D]. In most descriptive studies, >30 ng/mL is considered sufficient, 15–30 ng/mL is considered insufficient, and <15 ng/mL is considered deficient.

Table 1. Summary of Vitamin D function and biologic effect.

Function	Effect
Calcium and phosphorus homeostasis	Bone health
Cell growth and regulation	Anti-proliferation, apoptosis, cancer
Immune function	Multiple sclerosis, IBS , TIDM, psoriasis, RA
Renin-angiotensin regulation	Lowered risk for HF, TIIDM, HTN
Neuromuscular regulation	Muscle strength, balance

IBS–Inflammatory Bowel Disease; TIDM–Type I Diabetes Mellitus; RA–Rheumatoid Arthritis; HF–Heart Failure; TIIDM–Type II Diabetes Mellitus; HTN–Hypertension.

In patients with cardiovascular disease, survival was significantly lower in subjects with vitamin D deficiency [4,5]. Vitamin D deficiency has also been associated with glucose intolerance [6,7,12]. One study showed an increased risk for insulin resistance and metabolic syndrome with vitamin D deficiency [6]. Nikooyeh *et al*. found a significant inverse association between changes in 25(OH)D concentration and changes in BMI, weight, serum insulin, and Hb A1C [7]. The results showed that an improvement in 25(OH)D status in Type II DM is beneficial for glycemic and weight control [7]. An improvement in hemoglobin A1C of 1%–1.5% has been reported in diabetic patients with vitamin

D deficiency who were repleted. [14] In patients with asthma, reduced vitamin D concentrations were associated with airway hyper-responsiveness and reduced glucocorticoid response, and increasing vitamin D concentrations were associated with improved lung function [8] In another study, vitamin D insufficiency and deficiency were shown to be significantly associated with respiratory disease mortality [4]. Vitamin D is known to have multiple effects on immune function [3,15]. Ginde *et al*. reported that 25(OH)D status is inversely associated with upper respiratory tract infections and the association may be stronger in patients who have a respiratory tract disease [10]. Mortality in the general population was associated with a decrease by 8% for every 8 ng/mL increase in 25(OH)D concentration in a recent meta-analysis [11].

The high prevalence of vitamin D deficiency and the disease and mortality associated with it in the general population led to the concern that this disorder would be important in the critically ill. In this population there is a substantial amount of literature about vitamin D deficiency and its associated morbidity and mortality [16]. This review aims to highlight the prevalence of vitamin D deficiency in the critically ill population, assess the clinical implications of vitamin D deficiency, and evaluate the effects of vitamin D supplementation in this population.

2. Concentrations of Vitamin D and Clinical Outcomes in Observational Studies

Several studies have evaluated the effect of 25(OH)D sufficiency, insufficiency, and deficiency on morbidity and mortality in critically ill patients. All the studies cited here included either medical, surgical or trauma ICU patients. A summary of these studies is depicted in Table 2.

Table 2. Summary of studies evaluating the effect of vitamin D status in the critically ill population.

No. of Patients	Initial Serum 25(OH)D Status	No. of Patients	Percent of Patients (%)	Outcomes	Summary of Results
100 [16]	Normal	21	21.0	28-day mortality was not significantly different between the four groups	No significant association between 25(OH)D concentrations and length of ICU stay. 79% of patients had low 25(OH)D concentrations
	Insufficient	32	32.0		
	Deficient	26	26.0		
	Undetectable	21	21.0		
170 [17]	Severe septic patients (10.1 ng/mL) [a]	98	57.6	28-day mortality was not statically different between the two groups with rates of 27.9% in severe septic patients and 11.1% in trauma patients	No significant association between low 25(OH)D concentrations and outcomes
	Non-septic trauma patients (18.4 ng/mL)	72	42.4		
2,399 [18]	Sufficient	844	35.2	Adjusted 30-day morality odds ratio was 1.00, 1.36, and 1.69, respectively	Preadmission 25(OH)D deficiency is associated with mortality
	Insufficient	918	38.3		
	Deficient	637	26.6		

Table 2. *Cont.*

No. of Patients	Initial Serum 25(OH)D Status	No. of Patients	Percent of Patients (%)	Outcomes	Summary of Results
1,325 [19]	Sufficient	668	50.4	Adjusted 30-day mortality odds ratio was 1.00, 1.35, and 1.94 [b] respectively	25(OH)D deficiency is significantly associated with all-cause mortality
	Insufficient	472	35.6		
	Deficient	185	14		
2,075 [20]	Sufficient	769	37.1	Adjusted 30-day mortality odds ratio was 1.00, 1.41 [c], and 1.61 [d] ,respectively	Preadmission 25(OH)D deficiency is significantly associated with acute kidney injury and mortality
	Insufficient	804	38.7		
	Deficient	502	24.2		
100 [21]	Sufficient	21	21.0	Hospital-free days were significantly different between patients with deficiency and sufficiency [e]	Deficient patients had fewer hospital-free days. No significant relationship between 25(OH)D concentrations and mortality
	Insufficient	55	55.0		
	Deficient	24	24.0		
196 [22]	Sufficient	37	18.5	Mean time-to-alive at ICU discharge was 5.9 ± 5.4, 6.8 ± 6.0, and 10.6 ±8.4 respectively	25(OH)D insufficiency is associated with longer time-to-alive ICU discharge but was not associated with mortality
	Insufficient	109	55.9		
	Deficient	50	25.6		

[a]: $p < 0.0001$ compared to non-septic trauma patients; [b]: $p < 0.02$ compared to sufficient patients; [c]: $p < 0.01$ compared to sufficient patients; [d]: $p < 0.004$ compared to sufficient patients; [e]: OR 3.15 (1.18–8.43).

Two early prospective observational studies evaluated the effect of 25(OH)D concentrations on outcomes and mortality in critically ill patients [16,17]. The studies reported that there was no significant association between 25(OH)D concentrations with mortality and length of ICU stay. Nosocomial infections or hospital-acquired infections were not significantly different among those patients with vitamin D sufficiency or deficiency [16]. Limitations of this study include the short time frame for observation, limited sample size, and the lack of sequential vitamin D blood sampling. Cecchi *et al*. [17] found no significant difference in outcomes, including ICU length of stay and hospital length of stay, between patients with vitamin D sufficiency or deficiency. To limit age-related bias, a subgroup of trauma ICU patients was compared to a sepsis ICU group which had significantly lower vitamin D concentrations. These findings suggest that vitamin D may play an important role in sepsis pathology and therefore may have a role in outcome. The lack of significance found in these initial studies may be due to the limited number of patients.

Two large multiyear, multicenter observational studies assessed the relationship between 25(OH)D status in critically patients and 30-day mortality after ICU admission [18,19]. The major difference between the two studies is that the first study included patients who had 25(OH)D concentrations drawn 1 week to 1 year prior to ICU admission [18]. This allowed inference of a potential relationship between vitamin D and the onset of critical illness. The second study included patients who had 25(OH)D concentrations drawn 7 days prior or post admission. This allowed 25(OH)D concentrations

to be universally assessed at a relative point near the hospitalization [16]. Unmeasured variables may have influenced mortality independent of vitamin D status. Selection bias may be present since 25(OH)D concentrations may have been drawn for a reason that is not present in patients outside of the critical care population. Depressed 25(OH)D concentrations observed in the critically ill population could be caused by critical illness itself; thus, reverse causation may be present. However, the earlier study found that more severe 25(OH)D deficiency was also associated with increased mortality following critical care and could help explain the current findings [18]. A strength of the study is the large patient population which gives the results greater reliability. The studies found that preadmission and admission vitamin D deficiency in the critical care setting is significantly associated with an increased risk of death at 30-day. Vitamin D deficiency was also significantly associated with 90-day and 1-year mortality compared to those who were sufficient [18,19].

The vitamin D status of critically ill patients with acute kidney injury has also been evaluated [20] The primary endpoint was acute kidney injury using the RIFLE criteria occurring 7 days prior to or 7 days after hospitalization in a critical care unit [21]. Vitamin D deficiency was reported to be significantly associated with an increased risk of acute kidney injury in this patient population. After adjusting for age, gender, race, season, sepsis, and type of ICU patient (surgical or medical), it was reported that there was a risk of mortality 1.4 times higher in vitamin D insufficient patients and 1.6 times higher in deficient patients. Like the previous studies done by Braun *et al.* [20] these results showed a significant association between vitamin D deficiency and 30 day mortality.

Nair *et al*. conducted a multicenter cohort study to determine the prevalence of vitamin D insufficiency and deficiency and to analyze the association between these biochemical abnormalities and clinical outcomes [22]. This study reported on medical and surgical ICU patients with expected admissions lasting at least 2 days. On days 1, 3, and 7, 25(OH)D, 1,25 dihydroxyvitamin D [1,25$(OH)_2$D], parathyroid hormone (PTH), and ionized calcium were measured. Vitamin D insufficiency and deficiency were defined as 25(OH)D concentrations of 10–20 ng/mL and <10 ng/mL, respectively. These definitions included lower concentration ranges than some of the other studies previously conducted. However, the prevalence of both 25(OH)D insufficiency and deficiency were 56 and 25% respectively, similar to other studies. There was no significant change in 25(OH)D concentrations between days 1, 3, and 7 of ICU stay. The outcomes measured were ICU and hospital stay, ICU and hospital free days (HFD), and ICU and hospital mortality. ICU free days and HFD were the number of days the patient spent outside the ICU or hospital in the 28-day period following ICU admission. They reported a significant association between vitamin D deficiency and an increased severity of illness at ICU admission. 25(OH)D deficiency was significantly associated with fewer hospital free days; however, no significant association was found between vitamin D deficiency and mortality. The results of this study are similar to earlier reports [16,17]. All reported a high prevalence of vitamin D insufficiency and deficiency in the critically ill population. No significant association between vitamin D insufficiency or deficiency and mortality was observed. However, all three analyzed small patient populations which limit the power of the results [16,17,22]. Also, Nair *et al*. [22] reported an overall low mortality rate in their critically-ill patient population. This would make it even more difficult to detect a difference in mortality as it related to 25(OH)D concentrations.

A prospective study analyzed medical and surgical ICU patients in a tertiary care hospital to observe the trend of vitamin D status throughout a patient's ICU stay and the relationship between 25(OH)D concentrations and adverse clinical outcomes, particularly length of ICU stay, risk of infection, and mortality [23] Serum 25(OH)D concentrations were collected at time of admission and then repeated after 3 and 10 days of ICU stay [23] At admission, insufficient or deficient concentrations of 25(OH)D were observed in 82% of the patients. The mean 25(OH)D concentrations at baseline decreased significantly by day 3 ($p < 0.001$) and remained significantly decreased in patients who stayed 10 days or more in the ICU. In the vitamin D sufficient group at baseline, 39.1% of those patients developed insufficiency at some point while in the ICU. This is the first study to observe a statistically significant post-admission decrease in 25(OH)D concentrations during ICU stay. Patients who had sufficient 25(OH)D levels had a significantly shorter time-to-alive ICU discharge of 5.9 ± 5.4 days compared to 10.6 ± 8.4 days observed in deficient patients ($p < 0.01$). The study reported a trend toward higher rates of infection in insufficient and deficient 25(OH)D patients. Vitamin D status was not significantly associated with all cause 28-day mortality [23]. Insufficient sample size may be one reason that this study failed to observe clinical outcome results similar to previous reports [18,19]. Another limitation is confounding variables may be present that could not be accounted for in a multivariate analysis which means that the adverse clinical outcomes observed may not be the direct cause of low vitamin D concentrations.

All but two of these studies found a correlation between vitamin D deficiency and adverse clinical outcomes [18–20,22]. The two negative studies were both limited by the small sample size [12,16]. Braun *et al*., who included a large number of patients, found a significant association between low 25(OH)D concentrations and mortality [18–20]. More large studies of this nature are needed to confirm the results to date. The literature indicates there is a link between clinical outcomes and vitamin D status in the critically ill.

3. Vitamin D Supplementation

Although recent literature has highlighted the prevalence of vitamin D deficiency and linked it to adverse clinical outcomes, there is uncertainty about how to correct vitamin D deficiency in the critically ill setting. A small number of studies summarized in Table 3 evaluated the effect of vitamin D supplementation on serum 25(OH)D concentrations in this patient population [24–26].

For hospitalized patients, the current recommendation by the American Society for Parenteral and Enteral Nutrition is 200 international units (IU) of vitamin D (cholecalciferol, D2) daily by the intravenous route. This is considered a maintenance dose for this vitamin and does not take into account patients who are deficient or insufficient and need to be supplemented. The daily dose of 200 IU vitamin D (cholecalciferol) was shown to be ineffective in normalizing vitamin D concentrations of patients who were vitamin D deficient [24]. In this 10-day trial, serum concentrations of 25(OH)D were significantly higher on days 2,6, and 7 ($p < 0.05$) for a group receiving higher doses of vitamin D (500 IU of ergocalciferol, D3) daily compared to the standard dose of 200 IU cholecalciferol daily. Unfortunately, 25(OH)D serum concentrations remained below normal in all treatment groups during the 10 day trial. Using both vitamin D2 and D3 in this supplementation study was a confounding variable. Lower concentrations of 25(OH)D were observed in non-survivors in critically ill patients [24].

Table 3. Summary of studies evaluating the effect of vitamin D supplementation in the critically ill population.

No. of Patients	Treatment groups	Initial Serum 25(OH)D	Intervention	Outcome	Summary of Results
22 [24]	Critical Care Patients (N = 10)	10 ± 4.2 mcg/L	200 IU vitamin D IV	25(OH)D levels were higher in the high dose group on days 2, 6, and 7 [a]. No outcome available	25(OH)D levels were lower in the non-survivors compared with survivors [b]. Doses studied did not normalize 25(OH)D serum concentrations.
	Critical Care Patients (N = 12)	10 ± 4.2 mcg/L	500 IU vitamin D IV		
	Ambulatory Controls (N = 62)	20.1 ± 8.9 mcg/L	Placebo		
33 [25]	Group A (N = 12)	5.6 ± 2.2 ng/mL	Placebo	6.2 ± 2.8 ng/mL 25(OH)D	97% of critically ill patients were vitamin D deficient. Group B showed a statistically significant increase in 25(OH)D concentrations.
	Group B (N = 11)	3.7 ± 2.6 ng/mL	60,000 IU $25(OH)D_3$ PO	46 ± 16.5 ng/mL 25(OH)D [c]	
	Group C (N = 10)	5 ± 2.6 ng/mL	2 mcg $1,25(OH)_2D_3$ IV	5 ± 2.3 ng/mL 25(OH)D	
25 [26]	Vitamin D group (N = 12)	13.1 ng/mL	Single enteral dose of 540,000 IU vitamin D3 PO or per tube	38.2 ng/mL 25(OH)D [d,e]	The mean serum 25(OH)D increased in the treatment group 25 ng/mL. Deficiency was corrected in 2 days with no adverse effects.
	Placebo (N = 13)	14.1 ng/mL	Placebo	13.7 ng/mL 25(OH)D	

[a]: $p < 0.05$ compared to the standard-dose group; [b]: $p < 0.009$ between survivors and non-survivors; [c]: $p < 0.0001$ between baseline 25(OH)D and after 7 days of supplementation; [d]: $p < 0.05$ compared to baseline 25(OH)D for the supplemented group; [e]: $p < 0.05$ between day seven 25(OH)D concentrations in placebo group and supplemented group.

Larger doses of vitamin D were studied in two recent clinical trials. Mata-Granados *et al*. [25] administered two 60,000 IU 25(OH)D oral doses to a group of critically ill septic patients which resulted in a significant increase in serum 25(OH)D concentration from baseline, 4 ng/mL to 46 ng/mL 25(OH)D ($p < 0.0001$). A single oral dose of 540,000 IU of cholecalciferol was used to treat critically ill patients in a randomized, double-blind pilot study [26]. The aim was to correct vitamin D deficiency by achieving 25(OH)D levels of 30 ng/mL or greater by day 7. In the vitamin D supplemented group, the mean baseline 25(OH)D concentration was 13.1 ng/mL and it increased to a mean of 38.2 ng/mL on day 7 which was significantly greater than the placebo group in which no significant change was observed. (Table 3) Concentrations increased within 2 days after one mega-dose of cholecalciferol in most patients without causing adverse effects of hypercalcemia or hypercalcuria. The study also observed that daily maintenance doses of 200 IU of calciferol did not significantly affect 25(OH)D concentrations. The authors could not exclude that smaller more frequent doses would not be able to achieve the same results [26]. Clinical outcomes such as mortality could not be evaluated due to the small sample size. This is the first randomized controlled trial to study the short term effects of high-dose vitamin D in the critically ill population.

The recommended daily dose of 200 IU intravenously or even doubling that to 500 IU of vitamin D intravenously did not have any significant effects on serum 25(OH)D concentrations [24]. However, in the studies that evaluated the effect of larger doses, two oral doses of 60,000 IU and one oral dose of 540,000 IU 25(OH)D, demonstrated significant effects on elevating 25(OH)D concentrations [25,26]. Only short term effects have been evaluated in the ICU; thus, large randomized controlled trials are needed to determine the long-term effects and clinical outcomes of high-dose vitamin D supplementation. It is notable that a dose of 10,000 IU per day in healthy males is safe [27]. Monitoring for toxicity (e.g., hypercalcemia) would be prudent in patients receiving large doses of vitamin D.

4. Conclusion

Vitamin D insufficiency and deficiency are associated with poor clinical outcomes in all populations. These disorders are especially prevalent in critically ill patients. It is currently not clear how much of this disorder is contributed by pre-ICU vitamin D status and how much is caused by the complications of critical illness. Examples of the latter include alteration in protein binding of vitamin D or the effect of crystalloid or colloid resuscitation shortly after admission to the ICU. The data related to vitamin D deficiency and morbidity and mortality is varied, but in larger studies it has been associated with major adverse effects on clinical outcome and mortality. Intuitively, when a patient is deficient in a nutrient, a health-care provider would treat the deficiency. Questions remain about how treatment would affect outcomes and which dose of vitamin D would be effective with long term safety. More studies are needed to answer these questions.

Conflicts of Interest

The authors declare no conflict of interest.

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