Curr Gastroenterol Rep (2016) 18: 18
DOI 10.1007/s11894-016-0492-2

Vitamin D Status and Supplementation in the Critically Ill

T. J. McKinney[1] · Jayshil J. Patel[2] · Matthew V. Benns[1] · Nicholas A. Nash[1] · Keith R. Miller[1]

Published online: 7 March 2016

Abstract Vitamin D deficiency has recently been recognized as a widespread global disorder. Generally considered a direct extension of malnutrition, even subclinical hypovitaminosis D is now recognized in adequately nourished populations. Compared to the general population, the prevalence of hypovitaminosis D is greater in the critically ill population. In fact, several studies have shown poorer outcomes in critically ill patients discovered to be vitamin D deficient or insufficient. Controversy persists regarding vitamin D measurements, quantity of supplementation, and appropriate target level in various populations. Vitamin D has a vital role in calcium homeostasis and extra-skeletal health, such as immune function. Therefore, vitamin D supplementation may have a role for improving outcomes in critically ill patients. In this review, we will first discuss the metabolism and function of vitamin D under normal physiologic conditions. We will then explore the prevalence and prognostic value of vitamin D deficiency in critical illness. Finally, we will examine recent trials focusing on appropriate dosing, route of administration, and outcomes associated with vitamin D supplementation in the ICU.

Keywords Vitamin D · Vitamin D deficiency · Hypovitaminosis D · Malnutrition · Critical care · Intensive care

This article is part of the Topical Collection on *Nutrition and Obesity*

✉ Keith R. Miller
krmill10@louisville.edu

[1] Department of Surgery, University of Louisville School of Medicine, 550 South Jackson Street, Louisville, KY 20222, USA

[2] Department of Medicine, Division of Pulmonary & Critical Care Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

Introduction

Malnutrition, although defined using a variety of criteria, when identified in the setting of critical illness has long been associated with poor outcomes. Numerous vitamin and nutrient deficiencies have been described with catastrophic consequences in a multitude of settings but are often confined to case reports. Micronutrient deficiencies have historically been difficult to diagnose based on the subclinical phenotype associated with such conditions and are generally considered as one manifestation of severe malnutrition. Diagnosing micronutrient deficiency requires a high index of suspicion that may often be easily overlooked. In addition, assuring appropriately calibrated laboratory analysis for such deficiencies may be encumbering. When recognized, reversal of micronutrient deficiency can be rewarding as patient condition may dramatically shift towards a favorable outcome. On the contrary, critical illness may predispose an individual to micronutrient deficiency, resulting in an illness-specific or illness-related deficiency. Indeed, a pre-existing deficiency may compound the severity of the problem. Over the last several years, multiple studies have demonstrated that vitamin D deficiency is a pre-existing and acquired disorder in critical illness, and the prevalence is probably greater than once believed.

In 2009, Lee et al. first introduced the increased prevalence of vitamin D deficiency in critical illness [1]. This realization may have been delayed by the complex metabolism involved with vitamin D under normal physiologic circumstances, the limited availability and utility of vitamin D assays, and the fact that the majority of metabolites within the pathway are inactive. The proclivity for vitamin D deficiency hinging upon seasonal variation ultraviolet (UV) light exposure has been well-known, but clinical implications in the critically ill patient had not been realized, or even considered, until recently. A relevant point of discussion is whether vitamin D deficiency

is simply another marker for morbidity and mortality, or if increasing levels through exogenous vitamin D supplementation can improve outcomes through a biologically plausible mechanism. In this review, we will first discuss the metabolism and function of vitamin D under normal physiologic conditions. We will then explore the prevalence and prognostic value of vitamin D deficiency in critical illness. Finally, we will examine recent trials focusing on appropriate dosing, route of administration, and outcomes associated with vitamin D supplementation in critically ill patients.

Background: Structure and Function

Along with vitamins A, E, and K, vitamin D is recognized as a fat-soluble vitamin. Vitamin D is obtained by two distinct methods (Fig. 1). The first method is through oral intake. Except for fatty fish livers, very few foods contain vitamin D, but when ingested, it is absorbed primarily in the small bowel. It is then packaged in chylomicrons and moved through the liver to the systemic circulation. Oral intake can also be accomplished through supplementation in the form of ergocalciferol (vitamin D2) cholecalciferol (vitamin D3), or through specifically fortified nutritional options [2]. The second (and major) method of vitamin D acquisition is through dermal synthesis. UVB exposure through sunlight results in the conversion of 7-dehydrocholesterol to previtamin D3. This process can, at times, account for the large majority of the precursor to active vitamin D and is variable dependent upon ethnicity and sun exposure [3].

Vitamins D2 and D3 enter the hepatic circulation where they are converted to 25-hydroxycholecalciferol [25(OH)D] (or calcidiol) by the hepatocyte-derived enzyme vitamin D 25-hydroxylase. The product is transported in the plasma by vitamin D-binding protein. Further hydroxylation renders the biochemically active form of vitamin D. This hydroxylation step occurs primarily in the proximal tubules of the kidneys in response to circulating parathyroid hormone (PTH). The second hydroxylation results in the formation of calcitriol (1,25-dihydroxycholecalciferol), which is the most physiologically potent form of vitamin D. Due to the complexity of vitamin D metabolism, organ insufficiency at any step in the conversion process can result in reduced biochemical vitamin D activity.

Vitamin D is thought to be stored in part in adipose tissue. However, this relationship is complex, and liberalization from adipose tissue does not seem to be straightforward during times of deficiency or inadequate availability. Obese patients have increased potential for storage, but are not capable of vitamin D mobilization during times of stress. In addition, vitamin D metabolites may result in adipogenesis [4]. Interestingly, obese patients who subsequently lose weight have demonstrated increasing serum vitamin D levels. [5].

Vitamin D is most appreciated for the role it plays in calcium regulation, absorption, and metabolism. Regarding calcium homeostasis, vitamin D plays a role in increasing serum calcium concentration by a multitude of different mechanisms. First, it promotes the active intestinal absorption of calcium while also stimulating the active intestinal absorption of phosphate. Vitamin D is the only hormone known to induce the proteins involved in active intestinal calcium absorption. Second, vitamin D stimulates osteoblasts to synthesize receptor activator nuclear factor-κB ligand (RANKL). This nuclear factor promotes the formation of new osteoclasts and stimulates bone resorption, thereby increasing serum calcium levels [6]. It is important to note that vitamin D does not work alone

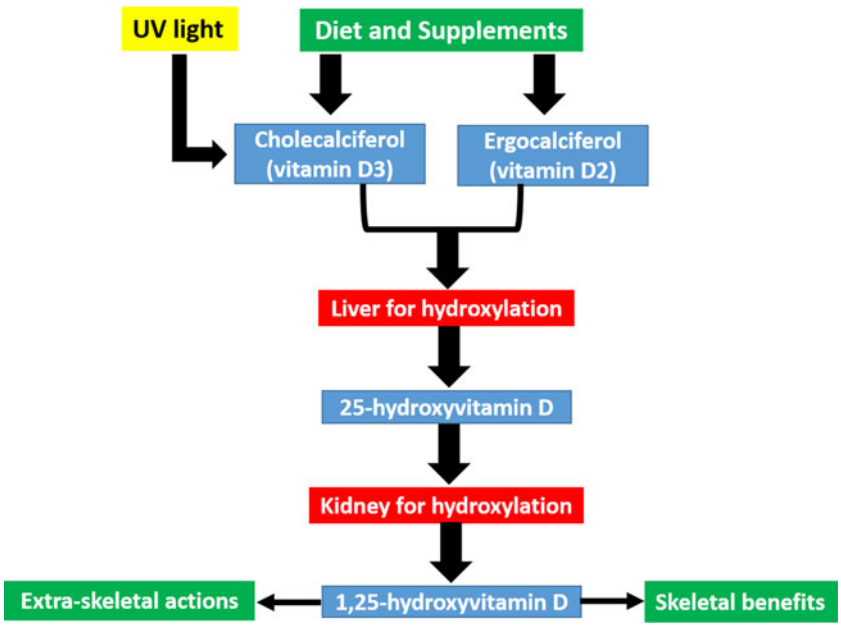

Fig. 1 Vitamin D pathway and benefits. Skeletal benefits include calcium and phosphate homeostasis and extra-skeletal actions include regulating immune function, cardiovascular health, and neuropsychiatric health. *UV* ultraviolet

in calcium and phosphate homeostasis, but works in conjunction with PTH to facilitate bone resorption.

Vitamin D receptors are present on nearly every body tissue suggesting the potential for a wide-range of biochemical properties and poorly understood physiologic implications. In addition to its well-established role in skeletal calcium homeostasis and intestinal absorption of calcium, vitamin D seems to be vital for a well-functioning innate and adaptive immune systems and cell differentiation. Nuclear vitamin D receptors are found on macrophages, B cells, and T cells [7]. In the immune system, binding of the nuclear vitamin D receptor to neutrophils results in an increased synthesis of antimicrobial peptides and defensin [8, 9]. Furthermore, vitamin D and its associated receptor have been demonstrated to exhibit anti-inflammatory and membrane-stabilizing characteristics at barrier sites such as the gastrointestinal tract, lung, and integumentary systems [10]. These properties have led to increasing interest with regard to impacting outcomes in critically ill patients through multiple mechanisms of action.

In summary, vitamin D has a complex metabolism with multiple inactive precursors. Multiple pathways in at least 3 organ systems are required to facilitate conversion of vitamin D precursors to the biologically active form of vitamin D. Nearly every tissue has the capability to interact with vitamin D. Finally, in addition to calcium homeostasis, vitamin D is an integral component in maintaining barrier and immune function.

Vitamin D Levels in the General Population, Hospitalized, and Critically Ill Patient

An estimated one billion individuals worldwide are vitamin D insufficient or deficient [11]. However, vitamin D deficiency is not exclusive to developing countries and socioeconomically depressed regions. UV exposure clearly impacts prevalence as equatorial regions generally experience less vitamin D deficiency. Contrary to popular belief, vitamin D deficiency is not confined to the elderly or malnourished. Illustrating this point, Maroon et al. looked at the vitamin D level of 80 professional athletes from the National Football League and observed low mean serum levels at 27 ng/ml. In addition, it was determined that players with higher vitamin D levels were more likely to obtain a contract position, suggesting some of the predictive characteristics of vitamin D levels in a very different arena [12].

Although these values from the aforementioned study appear low, it should be noted that there is controversy surrounding the appropriateness of threshold values attributed to define true deficiency. Endocrinologic societal guidelines classify a vitamin D level of <20 ng/ml as deficient and 20–30 ng/ml as insufficient. According to this definition, a level of 27 ng/ml would classify the elite athletes in the Maroon study to be insufficient. [13•]. However, the Institute of Medicine has concluded that levels >20 ng/ml are sufficient [14•], and using this definition, authors have noticed trends in over-supplementation in certain populations [15]. The 25-hydroxyvitamin D (25 (OH)D) and 1,25 dihydroxyvitamin D remain the most commonly assayed tests in the clinical setting to assess for vitamin D deficiency. There may be significant variability in assay methodology, and some immunoassays are vitamin D-binding protein concentration specific, somewhat limiting translatability of individual values [16]. These issues create difficulty interpreting the available literature and are likely impacted by the clinical setting. Regardless, given the evidence currently available, most experts are in agreement that vitamin D deficiency is not uncommon.

Clinical manifestations of vitamin D deficiency depend upon the severity and duration of the deficiency. Most patients with mild to moderate deficiency are asymptomatic, and serum calcium, phosphate, and alkaline phosphatase are normal. More severe and prolonged vitamin D deficiency leads to hypocalcemia and hypophosphatemia through reduced intestinal reabsorption and phosphaturia, respectively. Clinical symptoms include bone pain, muscle weakness, fatigue, and proclivity for fractures.

Given the high prevalence of vitamin D deficiency among "healthy" populations, it is not surprising that deficiency is widespread among hospitalized patients. Due to the complexity of metabolism and the requirement for some level of activation by multiple organ systems, pre-existing comorbidities are clearly associated with hypovitaminosis D. Increased prevalence has been observed but not limited to patients with renal insufficiency, chronic liver disease, inflammatory bowel disease, autoimmune disease, and metabolic syndrome [17–21]. One study indicated deficiency in more than half of the inpatient population on a medical service in the USA [22]. Taking this a step further, among the subset of critically ill patients, vitamin D insufficiency and deficiency have been demonstrated in greater than 20 and 60 % of patients, respectively, in the ICU setting [23]. Similar findings have been observed in pediatric ICU patients by the Canadian Critical Care Trials Group with vitamin D deficiency and insufficiency identified at rates of nearly 70 and 23 %, respectively [24]. Furthermore, the tissue demand for the most physiologically active form of vitamin D, 1,25-dihydroxycholecalciferol, increases during times of critical illness. The resulting inflammation, associated fluid shifts, and increased capillary permeability produce an alteration in vitamin D-binding protein and albumin levels that may impact serum levels and result in overestimation of true deficiency in the clinical setting [25].

The Prognostic Value of Vitamin D: Chicken or the Egg

Not surprisingly, given the increased scrutiny during recent years regarding the clinical relevance of vitamin D deficiency, multiple studies have demonstrated poorer outcomes

associated with low vitamin D levels in sepsis, surgical ICUs, and burn patients [26]. A multitude of earlier observational studies have shown an association with hypovitaminosis D and disease severity and mortality, hospital costs, ICU length of stay, amount of time requiring mechanical ventilation, infection rates, bacteremia, multisystem organ failure, discharge location, and both short- and long-term mortality [27–34].

Amrein et al. investigated the role of vitamin D deficiency with immune function and outcomes in critically ill patients. They sought to identify a correlation between serum 25-hydroxyvitamin D (25(OH) D) levels and hospital mortality rates, sepsis mortality, and the incidence of positive blood cultures. Utilizing a single-center, retrospective observation study, the 25-hydroxyvitamin D levels of 655 surgical and non-surgical critically ill intensive care patients were measured at a tertiary care center in Austria. Outcomes were controlled for age, gender, severity of illness, renal function, and relative inflammatory state. Within this patient population, only 13.6 % of critically ill patients were found to have normal range 25-hydroxyvitamin D level. Also, a significant association of decreased vitamin D levels was demonstrated in winter compared to summer months. The study concluded that a significant increase in adjusted hospital mortality rate was elucidated in those patients with low and intermediate 25-hydroxyvitamin D levels. Sepsis was the cause of death in 14.8 % of the deceased patients. There was no association between serum 25-hydroxyvitamin D levels and C-reactive protein, incidence of bacteremia, or white blood cell count [23]. Quraishi et al. attempted to establish whether the vitamin D status of critically ill patients was associated with longer hospital length of stays, 90-day hospital readmission rates, and 90-day all-cause mortality [34]. A prospective study was conducted at a single teaching institution in Boston examining 100 surgical ICU patients. Serum 25-hydroxyvitamin D levels were measured within 24 h of ICU admission. After adjusting for confounding variables, there was a significant association between total 25-hydroxyvitamin D levels and hospital readmission and overall mortality. The authors concluded that serum 25-hydroxyvitamin D levels obtained upon admission may help risk stratify to determine which patients may have an increased risk for longer hospitalizations, hospital readmission, and mortality. Similarly, results were observed in a smaller study of surgical ICU patients associating low vitamin D level with organ dysfunction, longer length of stay, and higher infection rates [35]. Additional studies have demonstrated similar correlations in pediatric ICU patients [24]. With regard to discharge disposition, patients with levels less than 20 ng/ml were found to be three times more likely to be discharged to a non-home location [31].

On the contrary, negative trials have also been published. Barnett et al. sought to establish an association between vitamin D levels with the incidence of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) in patients presenting with sepsis and trauma [36]. Utilizing 478 patients with sepsis and trauma with or without ALI/ARDS, two nested case–control studies were conducted. Initially, vitamin D levels were measured one day after ICU admission. After controlling for age, gender, diabetes, smoking status, and yearly season, the authors sought to determine if a relationship existed between low vitamin D levels and a primary outcome of incidence of ALI/ARDS during the first four ICU days. Secondary outcomes included hospital mortality and 1-year mortality. No association was demonstrated between vitamin D levels upon ICU admission and the development of ALI/ARDS, hospital mortality, or 1-year mortality in septic patients. However, lower vitamin D levels upon ICU admission were associated with significantly higher 1-year mortality in patients presenting with severe traumatic injury. In a study by Verceles et al., there were no differences in ventilator weaning between vitamin D deficient (<20 ng/ml) and vitamin D insufficient (>20 ng/ml) ICU survivors [37].

Interventional Trials

Despite the few dissenting negative trials discussed above, vitamin D deficiency in the majority of studies appears to be a valid prognostic indicator in the ICU. Can exogenous vitamin D administration to correct serum vitamin D level improve outcomes in critically ill patients? To this end, optimal vitamin D dose, route, and safety profile in ICU patients has been the objective of several recent interventional trials.

Vitamin D can be delivered through the enteral or parenteral route. Oral cholecalciferol (vitamin D_3), oral ergocalciferol (vitamin D_2) and IV calcitriol [1,25(OH)2 vitamin D_3] and cholecalciferol are commonly available forms in the clinical setting and have been investigated in recent trials. Each of these formulations requires different degrees of metabolism in order to become biochemically "active." The Institute of Medicine recommends vitamin D2 or D3 doses ranging 600 to 800 IUs (dependent upon age) per day (14). However, doses required to "correct" deficiency in the ICU are substantially higher, and initial studies have suggested that these "therapeutic" doses can be administered safely. Tolerance of higher doses is less surprising given approximately 10 minutes of summer UV exposure in Caucasians results in 10–20,000 IU of previtamin D released into the circulation over the following 24 h [38].

One of the earliest studies examining dosing concerns was conducted by Van den Berghe et al. and demonstrated little change in serum vitamin D levels with the administration of 200 and 500 IU cholecalciferol daily through the intravenous route [39]. Early studies in elderly patients demonstrated that 300,000–500,000 IU administered orally resulted in correction of vitamin D levels at 3 and 6 months post-administration [40, 41]. In the ICU, Mata-Granados et al. examined oral cholecalciferol given at 60,000 IU orally and

calcitriol (2 ug) administered intravenously and observed increased vitamin D levels in the oral group and little change in the intravenous group [42]. Leaf et al. observed a mixed response with regard to inflammatory markers with IV calcitriol administration in the ICU [43]. Given the findings of earlier studies, investigators continued to steadily increase the dose as pre-existing trials demonstrated acceptable safety profiles. Amrein et al. conducted a pilot study with 25 ICU patients receiving 540,000 IU of oral cholecalciferol and demonstrated normalization of serum levels in the large majority of patients within 48 h of administration [44]. This was subsequently followed by a large randomized controlled trial utilizing similar doses conducted by the same group (45). Considering that no supplementation occurs in the majority of ICUs in the USA, and "aggressive" units typically administer 200–800 IU per day, these are massive doses relative to current practice.

Administration of large dose of vitamin D appeared to be safe in the aforementioned trials. Vitamin D toxicity in the acute setting can result in hypercalcemia and hypercalciuria with cardiovascular and clinical consequences. Chronic vitamin D toxicity has similar ramifications in addition to diffuse organ and soft tissue calcification. Patients with pre-existing hyperparathyroidism would seem prone to hypercalcemia in the setting of exogenous vitamin D administration, but trials have suggested that this may not be the case with doses as high as 20,000 IU oral cholecalciferol administered weekly over a 3-month interval [45]. A recent study conducted in trauma patients demonstrated much higher rates of hypercalcemia than prior trials when administering 50,000 IU ergocalciferol orally up to three times per week. Hypercalcemia was observed in 25 % of patients in the highest dosing group (three times per week) even in the absence of correction of serum 25-OH vitamin D concentrations [46]. This finding suggests that there may be differences in ICU populations or the type of supplementation (ergocalciferol versus cholecalciferol) and that some caution is warranted in recommending vitamin D supplementation in all patient populations. Interpreting data on vitamin D deficiency in critical illness ought to take into account the population studied, dose provided, dosing interval, and the type of supplementation before implementation into clinical ICU practice (Table 1). Thus far, we have discussed the commonality of vitamin D deficiency in the ICU and the association of deficiency on outcomes and have reviewed trials demonstrating the positive and negative impacts of correcting vitamin D deficiency in ICU patients. Finally, the question remains regarding the impact of these interventions on clinical outcomes. To date, one such trial has attempted to answer the question: What is the impact of vitamin D supplementation on clinical outcomes in critically ill patients? In the VITdAL-ICU Randomized Clinical Trial, Amrein et al. sought out to determine the role of high-dose vitamin D supplementation in decreasing

Table 1 Trials examining supplementation of vitamin D

Author	Year	Population	Pts	Drug	Route	Dose	Findings	Adverse
Van den Berghe [39]	2003	ICU	22	Cholecalciferol	IV	200 IU 500 IU	Minimal change in serum markers	No hypercalcemia
Bacon [40]	2009	Elderly	63	Cholecalciferol	Oral	500,000 IU	Normalized levels	None
Von Restorff [41]	2009	Inpatient, elderly, rheumatology	33	Cholecalciferol	Oral	300,000 IU	Normalized vit D levels at 3 and 6 months	2 pts with mild hypercalcemia
Mata-Granados [42]	2010	ICU	33	Cholecalciferol Calcitriol	Oral IV	60,000 IU day 0/4 2 mcg	Normalized serum levels Little change	Not reported
Amrein [44]	2011	Medical ICU	25	Cholecalciferol	Oral	540,000	Corrected levels in most in 48 h	None
Leaf [43]	2014	Sepsis	67	Calcitriol	IV	2 mcg	Mixed reaction with inflammatory markers	None
Amrein [47••]	2014	ICU	475	Cholecalciferol	Oral	540,000 IU	No change in primary outcomes, Decreased hospital mort in deficiency	11 % serum Calcium > 10.6 mg/dL 1 patient serum Ca > 12 mg/dL
Rousseau [48]	2015	Burns	15	Cholecalciferol	IM	200,000 IU q 3 months for 12 months	Increased muscle strength, no change in bone health	No change corrected calcium
Dickerson [46]	2015	Trauma	65 16 18 31	Ergocalciferol	Oral	50,000 IU for 4 weeks Qweek 2× week 3× week	Percentage achieving normal levels 6 % 11 % 26 %	% serum ionized Ca concentration >1.34 mmol/L 13 % 6 % 23 %

hospital length of stay in vitamin D deficient ICU patients. Utilizing a randomized, double-blinded, placebo-controlled, single-center trial, a mixed medical and surgical population of nearly 500 adult intensive care unit patients were assigned to receive either 540,000 IU of cholecalciferol, the most physiologically active form of vitamin D, or placebo [46, 47••]. The dose of vitamin D3 was administered either orally or enterally via a nasogastric tube once, followed by monthly dosing (90,000 IU) for an additional 5 months. The primary outcome was hospital length of stay, while secondary outcomes included ICU length of stay, hospital mortality, and 6-month mortality. At the conclusion of the study, hospital length of stay was not significantly affected in patients receiving vitamin D3 supplementation when compared to placebo. In addition, there was no significant difference in hospital mortality or 6-month mortality. However, a significant decrease in hospital mortality rate was demonstrated in the severely deficient vitamin D subgroup when given supplemental vitamin D. This did not translate into a significant difference in 6-month mortality rates. Importantly, there were no serious safety events reported in the experimental group with 11 % developing mild hypercalcemia and one patient with serum calcium >12 mg/dL [47••] goes here as well).

Positive results in a secondary outcome in a single subgroup garnered from a single study make extrapolation difficult. However, these results are encouraging because severely deficient patients can be identified and treated with an inexpensive therapy with very minimal risk of adverse clinical events and the expectation of improved outcomes. Very few therapeutic adjuncts can assure as much, and there is clearly reason for cautious enthusiasm. At present, based on the above discussion addressing an issue that very much remains in evolution, a practical approach would involve assessment of serum vitamin D levels in critically ill patients with pre-existing risk factors early (upon admission) in their ICU course. Aggressive supplementation in those found to be severely deficient with 540,000 IU of oral/enteral cholecalciferol appears to be reasonably safe and achieves adequate serum targets in most patients. Serial daily assessment of serum calcium prior to and after supplementation is appropriate.

Conclusions

Vitamin D is an essential, fat-soluble vitamin involved in the maintenance of calcium homeostasis, skeletal health, and immunologic function. Vitamin D receptors are present in every tissue. Throughout the world, as many as one in six people may have subclinical vitamin D deficiency or insufficiency. In critical illness, vitamin D deficiency is exceedingly common, with prevalence reported as high as 85 %. In the ICU, associations between vitamin D deficiency and poor outcome variables have been observed. Vitamin D has multiple physiologic mechanisms; thus, it would seem evident that vitamin D supplementation has the potential to improve outcomes in the setting of trauma, severe burns, sepsis, and critical illness. Studies have demonstrated improvements in surrogate markers for inflammation. Much progress has been made over the last several years in determining the type and route of supplementation, dose, and dosing interval in specific ICU populations as well as the appropriateness of specific assays in determining true deficiency. Adverse events are reportedly rare although a more recent trial has suggested a higher incidence of hypercalcemia than observed in previous trials. A single prospective trial has demonstrated improvement with supplementation in a secondary study endpoint, albeit inpatient hospital mortality in severely deficient patients. Comprehension regarding the role of vitamin D supplementation in the ICU has improved markedly over the last several years, and there certainly remains reason for cautious enthusiasm. However, further investigation is necessary prior to widespread implementation in critically ill patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lee P, Eisman JA, Center JR. Vitamin D deficiency in critically ill patients. N Engl J Med. 2009;360(18):1912–4.
2. Amrein K, Christopher KB, McNally JD. Understanding vitamin D deficiency in intensive care patients. Intensive Care Med. 2015;41:1961–4.
3. Christopher KB. Vitamin D, supplementation in the ICU patient. Curr Opin Clin Nutr Metab Care. 2015;18(2):187–92.
4. Shivaprakash J. Mutt,1,2 Elina Hyppönen,3,4,5 Juha Saarnio,6 Marjo-Riitta Järvelin,2,7,8,9 and Karl- Heinz Herzig1,2,10, Vitamin D and adipose tissue—more than storage. Front Physiol. 2014; 5: 228
5. Rock CL, Jennifer JA, Flatt SW, Heath DD, Karanja N, Pakiz B, et al. Weight loss is associated with increased serum 25-hydroxyvitamin D in overweight or obese women. Obesity (Silver Spring). 2012;20(11):2296–301. doi:10.1038/oby.2012.57.
6. Quinn JM, Horwood NJ, Elliott J, Gillespie MT, Martin TJ. Fibroblastic stromal cells express receptor activator of NF-kappa B ligand and support osteoclast differentiation. J Bone Miner Res. 2000;15(8):1459–66.

7. Verstuyf A, Carmeliet G, Bouillon R, Mathieu C. Vitamin D: a pleiotropic hormone. Kidney Int. 2010;78(2):140–5.
8. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol. 2004;173(5): 2909–12.
9. Chun RF, Liu PT, Modlin RL, Adams JS, Hewison M. Impact of vitamin D on immune function: lessons learned from genome-wide analysis. Front Physiol. 2014;5:151.
10. Hewison M, Zehnder D, Chakraverty R, Adams JS. Vitamin D and barrier function: a novel role for extra-renal 1 alpha-hydroxylase. Mol Cell Endocrinol. 2004;215(1–2):31–8.
11. Holick MF. Vitamin D, deficiency. N Engl J Med. 2007;357(3): 266–81.
12. Maroon JC, Mathyssek CM, Bost JW, Amos A, Winkelman R, Yates AP Duca MA, et al. Vitamin D profile in National Football League players. Am J Sports Med. 2015;43(5):1241–5.
13.• Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30. Erratum in: J Clin Endocrinol Metab. 2011;96(12):3908. **Management guidelines from the Endocrine Society regarding Vitamin D deficiency in the inpatient and outpatient setting**.
14.• Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96(1):53–8. **This is an additional clinical reference discussing dietary reference intakes for calcium and vitamin D from the Institute of Medicine**.
15. McKenna MJ, Murray BF, O'Keane M, Kilbane MT. Rising trend in vitamin D status from 1993 to 2013: dual concerns for the future. Endocr Connect. 2015;4(3):163–71.
16. Heijboer AC, Blankenstein MA, Kema IP, Buijs MM. Accuracy of 6 routine 25-hydroxyvitamin D assays: influence of vitamin D binding protein concentration. Clin Chem. 2012;58(3):543–8.
17. Blair D, Byham-Gray L, Lewis E, McCaffrey S. Prevalence of vitamin D [25(OH)D] deficiency and effects of supplementation with ergocalciferol (vitamin D2) in stage 5 chronic kidney disease patients. J Ren Nutr. 2008;18(4):375–82.
18. Iruzubieta P, Terán Á, Crespo J, Fábrega E. Vitamin D deficiency in chronic liver disease. World J Hepatol. 2014;6(12):901–15.
19. Abou-Raya A, Abou-Raya S, Helmii M. The effect of vitamin D supplementation on inflammatory and hemostatic markers and disease activity in patients with systemic lupus erythematosus: a randomized placebo-controlled trial. J Rheumatol. 2013;40(3):265–72.
20. Pappa HM, Grand RJ, Gordon CM. Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease. Inflamm Bowel Dis. 2006;12(12):1162–74.
21. Miñambres I, Sánchez-Quesada JL, Vinagre I, Sánchez-Hernández J, Urgell E, de Leiva A, et al. Hypovitaminosis D in type 2 diabetes: relation with features of the metabolic syndrome and glycemic control. Endocr Res. 2015;40(3):160–5.
22. Thomas MK, Lloyd-Jones DM, Thadhani R, Shaw AC, Deraska DJ, Kitch BT, et al. Hypovitaminosis D in medical inpatients. N Engl J Med. 1998;338(12):777–83.
23. Amrein K, Zajic P, Schnedl C, Waltensdorfer A, Fruhwald S, Holl A, et al. Vitamin D status and its association with season, hospital and sepsis mortality in critical illness. Crit Care. 2014;18(2):R47.
24. McNally JD, Menon K, Chakraborty P, Fisher L, Williams KA, Al-Dirbashi OY, et al. The association of vitamin D status with pediatric critical illness. Pediatrics. 2012;130(3):429–36.
25. Ghashut RA, Talwar D, Kinsella J, Duncan A, McMillan DC. The effect of the systemic inflammatory response on plasma vitamin 25 (OH) D concentrations adjusted for albumin. PLoS One. 2014;9(3): e92614.
26. Rousseau AF, Foidart-Desalle M, Ledoux D, Remy C, Croisier JL, Damas P, et al. Effects of cholecalciferol supplementation and optimized calcium intakes on vitamin D status, muscle strength and bone health: a one-year pilot randomized controlled trial in adults with severe burns. Burns. 2015;41(2):317–25.
27. Braun AB, Litonjua AA, Moromizato T, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and acute kidney injury in the critically ill. Crit Care Med. 2012;40(12):3170–9.
28. Braun AB, Gibbons FK, Litonjua AA, Giovannucci E, Christopher KB. Low serum 25-hydroxyvitamin D at critical care initiation is associated with increased mortality. Crit Care Med. 2012;40(1):63–72.
29. Youssef D, Bailey B, El Abbassi A, Copeland R, Adebonojo L, Manning T, et al. Healthcare costs of Staphylococcus aureus and Clostridium difficile infections in veterans: role of vitamin D deficiency. Epidemiol Infect. 2010;138(9):1322–7.
30. Thickett DR, Moromizato T, Litonjua AA, Amrein K, Quraishi SA, Lee-Sarwar KA, et al. Association between prehospital vitamin D status and incident acute respiratory failure in critically ill patients: a retrospective cohort study. BMJ Open Respir Res. 2015;2(1): e000074.
31. Brook K, Camargo CA, Christopher KB, Quraishi SA. Admission vitamin D status is associated with discharge destination in critically ill surgical patients. Ann Intensive Care. 2015;5(1):23.
32. Sriram K, Perumal K, Alemzadeh G, Osei A, Voronov G. The relationship between immediate preoperative serum 25-hydroxyvitamin D_3 levels and cardiac function, dysglycemia, length of stay, and 30-d readmissions in cardiac surgery patients. Nutrition. 2015;31(6):820–6.
33. Higgins DM, Wischmeyer PE, Queensland KM, Sillau SH, Sufit AJ, Heyland DK. Relationship of vitamin D deficiency to clinical outcomes in critically ill patients. JPEN J Parenter Enteral Nutr. 2012;36(6):713–20.
34. Quraishi SA, Bittner EA, Blum L, McCarthy CM, Bhan I, Camargo Jr CA. Prospective study of vitamin D status at initiation of care in critically ill surgical patients and risk of 90-day mortality. Crit Care Med. 2014;42(6):1365–71.
35. Flynn L, Zimmerman LH, McNorton K, Dolman M, Tyburski J, Baylor A, et al. Effects of vitamin D deficiency in critically ill surgical patients. Am J Surg. 2012;203(3):379–82. discussion 382.
36. Barnett N, Zhao Z, Koyama T, Janz DR, Wang CY, May AK, et al. Vitamin D deficiency and risk of acute lung injury in severe sepsis and severe trauma: a case–control study. Ann Intensive Care. 2014;4(1):5.
37. Verceles AC, Weiler B, Koldobskiy D, Goldberg AP, Netzer G, Sorkin JD. Association between vitamin D status and weaning from prolonged mechanical ventilation in survivors of critical illness. Respir Care. 2015;60(7):1033–9.
38. Hollis BW. Assessment and interpretation of circulation 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in the clinical environment. Endocrinol Metab Clin North Am. 2010;39:271–86.
39. Van den Berghe G, Van Roosbroeck D, Vanhove P, Wouters PJ, De Pourcq L, Bouillon R. Bone turnover in prolonged critical illness: effect of vitamin D. J Clin Endocrinol Metab. 2003;88(10):4623–32.
40. Bacon CJ, Gamble GD, Horne AM, Scott MA, Reid IR. High-dose oral vitamin D3 supplementation in the elderly. Osteoporos Int. 2009;20(8):1407–15. doi:10.1007/s00198-008-0814-9.
41. von Restorff C, Bischoff-Ferrari HA, Theiler R. High-dose oral vitamin D3 supplementation in rheumatology patients with severe vitamin D3 deficiency. Bone. 2009;45(4):747–9.
42. Mata-Granados JM, Vargas-Vasserot J, Ferreiro-Vera C, de Castro MD L, Pavón RG, Quesada Gómez JM. Evaluation of vitamin D

endocrine system (VDES) status and response to treatment of patients in intensive care units (ICUs) using an on-line SPE-LC-MS/MS method. J Steroid Biochem Mol Biol. 2010;121(1–2):452–5.

43. Leaf DE, Raed A, Donnino MW, Ginde AA, Waikar SS. Randomized controlled trial of calcitriol in severe sepsis. Am J Respir Crit Care Med. 2014;190(5):533–41.
44. Amrein K, Sourij H, Wagner G, Holl A, Pieber TR, Smolle KH, et al. Short-term effects of high-dose oral vitamin D3 in critically ill vitamin D deficient patients: a randomized, double-blind, placebo-controlled pilot study. Crit Care. 2011;15(2):R104.
45. Rathi MS, Gonzalez S, Wright D, Ellis NR, Peacey SR. Management of hypovitaminosis D in patients with primary hyperparathyroidism. J Endocrinol Investig. 2014;37(5):467–71.
46. Dickerson RN, Berry SC, Ziebarth JD, Swanson JM, Maish 3rd GO, Minard G, et al. Dose-response effect of ergocalciferol therapy on serum 25-hydroxyvitamin D concentration during critical illness. Nutrition. 2015;31(10):1219–23.
47.•• Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA. 2014 Oct 15;312(15):1520–30. Erratum in: JAMA. 2014;312(18):1932. **This is the largest randomized controlled trial to date examining vitamin D administration in the ICU. There was no difference in primary outcomes when vitamin D administration was compared with placebo**.
48. Rousseau AF, Damas P, Ledoux D, Cavalier E. Effect of cholecalciferol recommended daily allowances on vitamin D status and fibroblast growth factor-23: an observational study in acute burn patients. Burns. 2014;40(5):865–70.