Nutrition 61 (2019) 173–178

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review article

Vitamin D in the ICU: More sun for critically ill adult patients?

Pascal L. Langlois M.D. [a,*], Frédérick D'Aragon M.D., Ph.D. [a], William Manzanares M.D., Ph.D. [b]

[a] Department of Anesthesiology and Reanimation, Faculty of Medicine and Health Sciences, Sherbrooke University Hospital, Sherbrooke, Québec, Canada
[b] Department of Critical Care, Intensive Care Unit, University Hospital, Faculty of Medicine, UDELAR, Montevideo, Uruguay

ARTICLE INFO

Article History:
Received 2 July 2018
Received in revised form 7 November 2018
Accepted 11 November 2018

Keywords:
Vitamin D
Cholecalciferol
Intensive care
Critical care

ABSTRACT

Critical illness in patients is characterized by systemic inflammation and oxidative stress. Vitamin D has a myriad of biological functions relevant to this population, including immunomodulation by the alteration of cytokine production and nuclear factor loop amplification. Low serum levels have consistently been found in observational studies conducted on critically ill patients, but the causality with mortality and worse outcomes has not been confirmed. The current focus is on interventional trials, whereas the pharmacokinetic profile of vitamin D administration remains sparse and the optimal strategy has not been confirmed. So far, high-dose oral or enteral supplementation is the most studied strategy. The largest randomized controlled trial published so far, the VITdAL-ICU (Effect of High-dose Vitamin D3 on Hospital Length of Stay in Critically Ill Patients with Vitamin D Deficiency) trial, showed no benefits on mortality in its primary analysis. However, secondary analysis suggested improvement in those patients with severe deficiency (i.e., 25-dihydroxyvitaminD <12 ng/mL). Smaller trials investigated intramuscular and intravenous administration and found interesting intermediate biochemical findings, including increased cathelicidins, but were not powered to investigate relevant clinical outcomes in the critically ill. The latest meta-analysis, which was recently published, does not support benefits of vitamin D supplementation in the heterogeneous population of critically ill patients. The European guidelines, published in the last year, suggest supplementing severely deficient patients with levels <12.5 ng/mL within the first week after ICU admission. However, other societies do not support such supplementation in their older recommendations. Large trials are currently recruiting ICU patients and could elucidate potential clinical benefits of vitamin D therapy in the critically ill.

Introduction

Over the past decade, the body of literature regarding micronutrient supplementation in critically ill patients has grown because of the frequent association of severe depletion of vitamins and trace elements with systemic inflammation and multiorgan failure. Vitamin D is a fat-soluble vitamin synthesized in the skin from 7-dehydrocholesterol before being converted in the liver and the kidneys to its most active metabolite, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], or calcitriol [1]. In 2011, the Endocrine Society's Clinical Practice Guidelines recommended serum levels >30 ng/mL as optimum for the general population [2], whereas vitamin D deficiency was defined as 25(OH)D <20 ng/mL, and vitamin D insufficiency as 25(OH)D 21–29 ng/mL [2]. Similarly, the Institute of Medicine defined vitamin D deficiency as serum levels <20 ng/mL [3]. Regardless of the definition, observational trials have demonstrated that the vast majority of patients hospitalized in the intensive care unit (ICU) are vitamin D depleted [4]. In an observational, retrospective study including 655 ICU patients, Amrein et al. found that 60.2% exhibited 25(OH)D levels <20 ng/mL and as many as 86.5% had <30 ng/mL [4]. In the United States, Dickerson et al. conducted a similar analysis on 158 critically ill adult patients with traumatic injuries admitted to the ICU [5]. The authors reported that 121 patients (77%) were deficient, of which 46 (38%) were severely deficient, and 31 (20%) showed insufficiency, with a 25(OH)D serum level <30 ng/mL. In Brazil, despite the sun exposure, a recent study reported a very high incidence of vitamin D deficiency at ICU admission, reaching 91.6% of patients. Interestingly, black patients had lower levels than whites owing to skin melanin concentration, whereas no difference were found between patients admitted in winter and other seasons. Finally, authors examined how healthy blood donor levels of both calcitriol and 25(OH)D varied in comparison with ICU patients [6]

All authors contributed to the conception and design of this manuscript. PLL wrote the first draft. WM and FDA critically revised the manuscript. All authors gave final approval for this submission and agree to be accountable for all aspects of work ensuring integrity and accuracy. The authors have no conflicts of interest to declare.

* Corresponding author: Tel.: +1 819 346 1110; Fax: +1 819 820 6413.
E-mail address: Pascal.laferriere-langlois@usherbrooke.ca (P.L. Langlois).

https://doi.org/10.1016/j.nut.2018.11.001
0899-9007/

to compensate for the high prevalence of deficiency in the general population. In agreement with previous findings, the prevalence of vitamin D deficiency was significantly higher in the ICU patients, reaching 96.7%, compared with 67% in healthy donors. It must be emphasized that, depending on the geographical latitude of the studied population, serum levels in a healthy non-ICU population can vary greatly, and therefore prevalence of vitamin D deficiency in an ICU population should always be compared with the general population of the same region [1]. Considering the various biological effects of vitamin D, the deficiency found in critically ill patients is of notable interest.

Biological effects

The biological effects of vitamin D are vast and go well beyond its effect on bones and calcium metabolism (Fig. 1). Apart from cardiovascular and autoimmune diseases, vitamin D contributes to immunomodulation and infection control, which are paramount in critically ill patients [1]. After transformation in the skin to vitamin D_3, it is metabolized to 25(OH)D by the liver [1]. The kidneys will further metabolize it to 1,25$(OH)_2$D, or calcitriol, the most active metabolite of vitamin D, with a shorter half-life. 25(OH)D is the major circulating form and represents the equilibrium between formation and clearance. The frequent presence of vitamin D receptors in various tissues confirms the diverse effects of vitamin D in the human body. In the macrophage, calcitriol will link the nuclear vitamin D receptor, which will migrate to express mRNA for cathelicidins, an antimicrobial peptide for host defense in barrier tissues of the gastrointestinal tract, airway, and bladder (Fig. 2). hCAP-18 and LL-37 are part of the cathelicidins family and have been studied as biomarkers for functional response of vitamin D supplementation [7]. Calcitriol also links the suppressor of cytokine signaling 1 to inhibit the activation of P38 mitogen-activated protein kinases and the nuclear factor-κB, responsible for loop amplification of cytokine expression and inflammatory response. The net effect is a reduced expression of tumor necrosis factor-α, interleukin (IL)-6, and monocyte chemoattractant protein-1, which can limit the overreactivity of inflammation pathways in critically ill patients [8]. The development of metabolomics, which analyze the alteration of intrinsic metabolic pathways in the human body, confirmed the differential metabolic profiles during critical illness according to vitamin D status [9] and could elucidate the broad effect of vitamin D on nuclear transcription and cell-cycle reduction. Glutathione and glutamate pathway metabolisms were significantly modified when vitamin D deficiency occurred, influencing the redox regulation and the immunomodulation of these pathways. Several animal trials confirmed the influence of vitamin D in the presence of systemic inflammation. Calcitriol exhibited a beneficial effect on lipopolysaccharide-induced acute lung injury in a murine model, notably on lung permeability, as evidenced by using Evans blue dye [10]. Despite the high prevalence of deficiency in critically ill patients, few studies addressed the underlying biological explanation. An observational protocol has recently been published and aims to identify whether acute kidney injury, often present in critically ill patients, is partly responsible for the high prevalence of vitamin D deficiency in the ICU [11].

Observational trials

The question remains: How does this deficiency translate to clinical outcomes? A large-scale meta-analysis of nearly 60 000 patients was published in 2012 by Zittermann et al. [12]. This systematic review and meta-analysis included prospective cohort studies with follow-up periods ranging from years to decades and confirmed that optimal levels of 25(OH)D were 28 to 35 ng/mL for overall survival. Low levels were associated with both increased mortality in the general population (relative risk [RR], 0.71; 95%

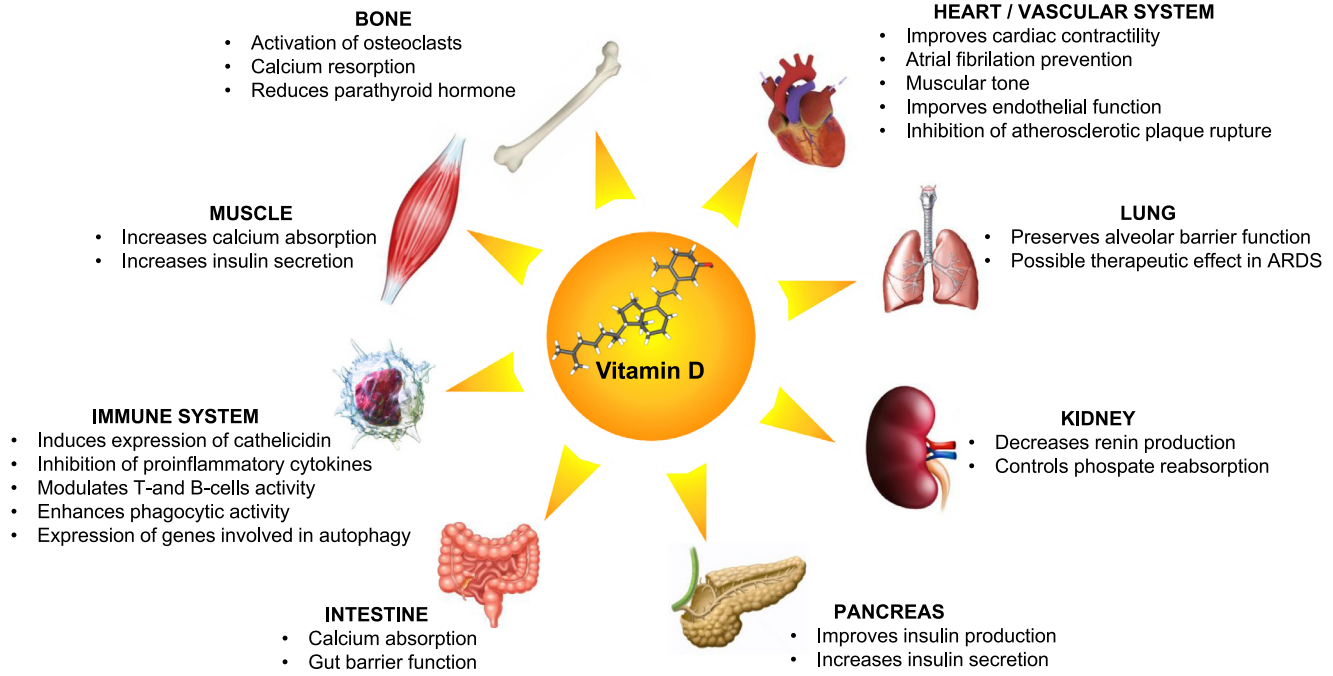

Fig. 1. Biological effects of vitamin D in healthy subjects and ICU patients. ARDS, acute respiratory distress syndrome.

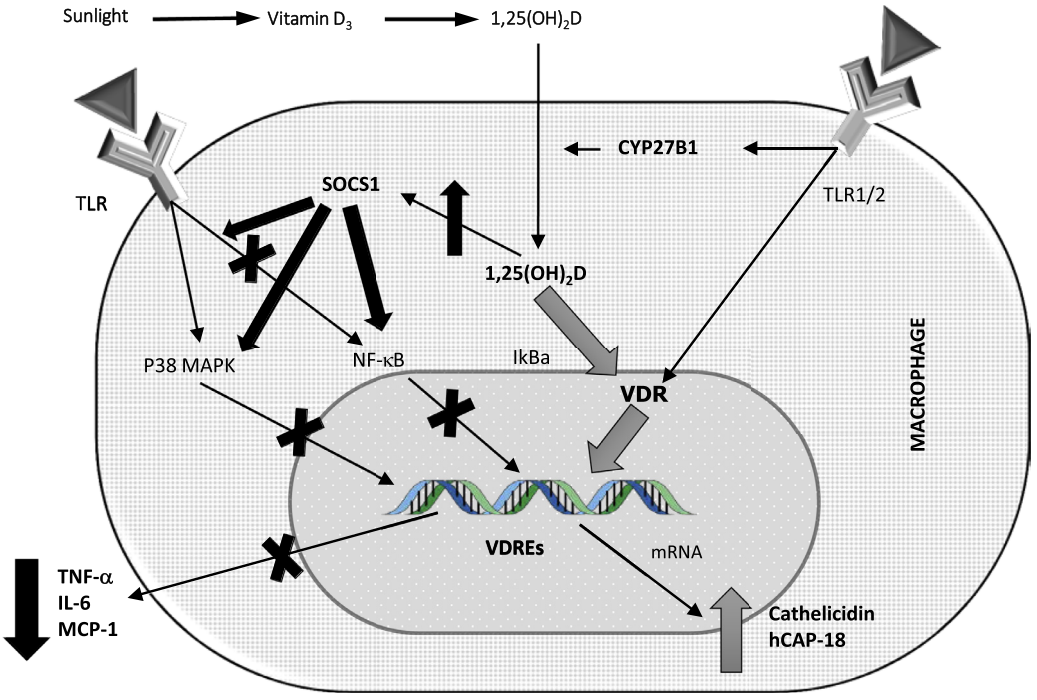

Fig. 2. Immunomodulatory effects of vitamin D in macrophages. CYP27B1, cytochrome p450 27B1; hCAP-18, human antimicrobial cathelicidin-18; IL6, interleukin; MAPK, mitogen-activated protein kinase; MCP, monocyte chemoattractant protein; NF, nuclear factor; SOCS1, suppressor of cytokine signaling 1; TLR, toll-like receptor; TNF, tumor necrosis factor a; VDR, vitamin D receptor; VDRE, vitamin D response element.

confidence interval [CI], 0.50–0.91), and increased incidence of infectious complications [12–14].

Similar data were reported specifically for ICU patients. The same 655 previously mentioned patients studied by Amrein et al. showed in a retrospective analysis that the adequate absolute level of 25(OH)D was associated with an increased cumulative chance of survival ($P = 0.034$) [4]. Furthermore, when ICU patients were divided in tertiles according to their serum levels, the highest tertile was associated with increased survival ($P = 0.004$). The authors also found that septic patients presented significantly lower levels of calcitriol, with a mean value of 12.3 ± 5 ng/mL. These data are in line with previous findings, which reported that after adjustment for Acute Physiological and Chronic Evaluation II (APACHEII) and demographic data, in-hospital mortality, 30-d mortality, and 90-d mortality were all significantly increased in 568 septic patients when 25(OH)D levels were <30 ng/mL with adjusted odds ratios (OR) of 1.62, 1.55, and 1.63, respectively [15]. The risk for sepsis also was significantly increased in ICU patients with 25(OH)D levels <15 ng/mL (OR, 1.51; 95% CI, 1.17–1.94) [15]. Another article retrospectively analyzed 24 94 adults hospitalized in the ICU between 1993 and 2011 [16]. After adjustment for age, sex, race, medical or surgical patient, season, and Deyo-Charlson Index, a U-shaped relationship existed between 25(OH)D levels and 90-d mortality. When compared with patients with levels between 30 and 49.9 ng/mL, patients with <10 ng/mL had a mortality RR of 2.01 (95% CI, 1.68–2.40) and, interestingly, those with a 25(OH)D concentration >70 ng/mL had a mortality RR of 1.69 (95% CI, 1.09–2.61). Mayr et al. compared cirrhotic and noncirrhotic patients in an observational study to analyze how hepatic disease could exacerbate the mortality associated with vitamin D deficiency. Once again, a high incidence of 25(OH)D deficiency (group <10 ng/mL = 55%; group 10–20 ng/mL = 23%) was found. Vitamin D status correlated with APACHE II, sequential organ failure assessment, and Child-Pugh scores. Levels <10 ng/mL correlated with 180-d mortality (hazard ratio, 2.45) and cirrhotic patients had a higher risk for mortality when the deficiency was severe (i.e., <10 ng/mL) [17]. Nonetheless, data is not so straightforward and several recent observational trials found no association between 25(OH)D levels and relevant clinical outcomes for ICU patients such as mortality and infections [18–21] or failed to demonstrate any relationship with mortality when analyzed in multivariate analysis [19].

Apart from mortality, vitamin D deficiency has been linked to adverse outcomes, including hospital-acquired pressure injuries, with an OR of 2 when 25(OH)D values were <20 ng/mL [22]. Brook et al. demonstrated that surgical patients' 25(OH)D levels measured within the first 24 h after ICU admission were correlated with the Functional Status Score for the ICU (FSS-ICU) at ICU discharge [23]. In this retrospective analysis, 25(OH)D levels <20 ng/mL were associated with a more than threefold risk for low FSS-ICU (score <17) compared with patients with 25(OH)D levels >20 ng/mL (OR, 3.45; 95% CI, 1.96–6.08). Furthermore, Gomes et al. demonstrated a very strong correlation between 25(OH)D concentration, especially when <12 ng/mL, and the prognostic indicator Charlson Comorbidity Index when adjusted for age, sex, and body mass index (OR, 1.59; 95% CI, 1.10–2.34) [24]. Moreover, the authors found an inverse correlation between 25(OH)D levels and cancer (OR, 3.42; 95% CI, 1.21–9.64) and acute liver failure (OR, 9.64; 95% CI, 2.28–40.60). No associations were found regarding duration of mechanical ventilation or mortality.

Therefore, vitamin D deficiency is both prevalent and relevant in ICU patients, but the literature remains sparse regarding the benefits of supplementing vitamin D in its various forms.

What have clinical trials found to date?

Through observational trials, it remains impossible to discern causality from a simple epiphenomenon. Despite the varying strategies, the most effective means of evaluating a causality effect of vitamin D deficiency on clinical outcomes is to administer supplementation in randomized controlled trials (RCTs) and observe outcomes. Several recent trials tempted strategies of vitamin D supplementation in ICU patients (Table 1). Notwithstanding, many questions about timing, route of supplementation, dose as pharmaconutrition strategy, and duration of therapy remain unanswered. One of the major difficulties of current research on vitamin D therapy in the critically ill is the limited knowledge regarding pharmacokinetic profile, the biomarkers to assess both vitamin D functional deficiency and functional repletion, and various heterogeneous supplementation strategies among RCTs published. All trials discussed so far used either calcitriol or 25(OH)D as a serum marker to assess functional levels of the vitamins. An interesting RCT by Leaf et al. suggested that cathelicidins (hCAP-18), a protein highly expressed after activation of nuclear vitamin D receptor, is a stronger predictor of 90-d mortality than total, bioavailable, or free 25(OH)D [25]. In 121 patients observed prospectively, the tertiles with lowest and intermediate hCAP-18 at ICU day 1 had significantly increased sepsis incidence (adjusted OR, 2.54 and 3.72, respectively), whereas 25(OH)D did not. Interestingly, the scope of the effect was lower in the first tertile than in the second, which opposes criteria of causality.

Nair et al. administered a single intramuscular dose of 150 000 or 300 000 IU of cholecalciferol to ICU patients with systemic inflammation and APACHE II score of 15 to 30 [26]. The two groups were initially deficient (21 and 17 ng/mL, respectively) and exhibited an increase in 25(OH)D levels after supplementation. The biomarker LL-37, a protein from the human cathelicidins family, presented a correlated increase with 25(OH)D at days 1 and 3, whereas the best correlation was between a 25(OH)D increase and an IL-6 decrease [26]. The trial was not powered to evaluate clinical outcomes and mortality was identical in both groups (n = 5/25). Another supplementation strategy was intravenous administration of 2 ug of calcitriol in patients with severe sepsis or septic shock [25]. No significant changes were noted in absolute serum levels of hCAP-18, IL-6, or other interleukins, but the mRNA for hCAP-18 and IL-18 were both significantly increased, with a correlation between $1,25(OH)_2D$ and hCAP-18 mRNA increase ($P = 0.003$). The trial was not powered to evaluate clinical outcomes. Other supplementation strategies included oral or enteral administration of cholecalciferol [27–29].

Over the past decade, six RCTs (Table 1) addressed this research question and recent meta-analyses were conducted for ICU patients [30,31]. Most of the trials had small numbers of patients and therefore, the effect is mostly driven by the VITdAL-ICU (Effect of High-dose Vitamin D3 on Hospital Length of Stay in Critically Ill Patients with Vitamin D Deficiency) trial conducted in 2014 [27]. In this trial, Amrein et al. recruited 475 adults with an expected ICU stay >48 h and 25(OH)D levels <20 ng/mL in five ICUs from a single center. The intervention arm received a loading dose of 540 000 IU of cholecalciferol followed by a maintenance dose of 90 000 IU every month for 5 mo. In the overall statistical analysis, no benefits were found regarding mortality (ICU, 28-d, hospital, 6-mo), ICU or hospital length of stay (LOS), or infectious complications. Early biochemical outcomes were unchanged (baseline, days 3 and 7) apart from an increase in 25(OH)D serum levels. At day 28, a reduction in C-reactive protein (51 versus 31 mg/L) and procalcitonin (0.2 versus 0.1 ng/mL) as well as an increase in albumin (3.13 versus 3.25 g/dL) were found. At 6 mo, no change persisted and biochemical analysis normalized in both arms. Interestingly, when data was restricted to patients with severe vitamin D deficiency defined by 25(OH)D <12 ng/mL, improvement in mortality was found at day 28 (23 versus 34%), in-hospital (28% versus 47%), and persisted at 6 mo (34.7% versus 50%). Finally, no subgroup of patients seemed to benefit more from intervention, including septic, cardiovascular, or neurologic patients. A recent RCT evaluated how a single pre-esophagectomy dose of 300 000 IU of cholecalciferol improved the postoperative pulmonary conditions [32]. The authors concluded that this high dose improved postoperative pulmonary vascular index, but not the extravascular lung water index. No improvement was found regarding 28- and 90-d mortality. In 2017, the protocol for the VITDALIZE (Effect of High-dose Vitamnin D3 on 28-day Mortality in Adult Critically Ill Patients) study was published. In this multicenter, international RCT, the authors aim to recruit 2400 patients with severe vitamin D

Table 1
Randomized controlled trials supplementing vitamin D in critically ill patients

Clinical trial [reference number]	Sample size (n)	Intervention	Main findings
Amrein et al. 2011 [28]	25	540 000 IU of vitamin D (cholecalciferol 13, 5 mg) orally or enterally	Confirmation of a single dose is to correct vitamin D deficiency. No changes in clinical outcomes.
Leaf et al. 2014 [25]	67	A single IV dose of calcitriol 2 μg	Higher hCAP-18 and IL-10 mRNA expression in intervention arm. No changes in clinical outcomes.
Amrein et al. 2014 [27]	492	540 000 IU of vitamin D_3 (cholecalciferol 13, 5 mg) PO or enterally	No effects on mortality, ICU and hospital LOS in overall analysis. Improvement of hospital, 28-d and 6-mo mortality in patients with severe deficiency (<12 ng/mL).
Quraishi et al. 2015 [29]	30	High dose: 400 000 IU cholecalciferol PO or enterally Low dose: 200 000 IU cholecalciferol PO or enterally	Changes in bioavailable 25(OH)D are associated with circulating LL-37, but not overall 25(OH)D. No changes in inflammatory markers or on clinical outcomes.
Nair et al. 2015 [26]	50	Two doses of 300 000 IU IM cholecalciferol vs standard therapy received a single dose of 150 000 IU of IM cholecalciferol	Increase in 25(OH)D levels were correlated to increase in cathelicidin at days 1 and 3. No changes in inflammatory markers or on clinical outcomes.
Han et al. 2016 [35]	31	High dose: 100 000 IU daily for 5 d (500,000 IU total dose) PO Low dose: 50 000 IU daily for 5 d (250,000 IU total dose) PO	Significant reduction in hospital LOS with proportional increment to dose. No changes on other clinical outcomes. No changes in LL-37 levels.
Parekh et al. 2018 [32]	79	A single oral pre-esophagectomy dose of 300 000 IU	Correction of 25(OH)D concentrations. Reduced postoperative pulmonary vascular permeability index. No change in extravscular water index

25(OH)D: 25-hydroxyvitamin D; hCAP, human cathelicidin antimicrobial protein; ICU, intensive care unit; IL, interleukin; IM, intramuscularly; IV, intravenous; LL-37, human cathelicidin, LL-37; LOS, length of stay; PO, per os, orally

deficiency (i.e., 25[OH]D <12 ng/mL) and administer either high-dose oral or enteral vitamin D_3 or placebo to evaluate 28-d mortality as the primary outcome. The trial is currently recruiting ICU patients and aims for completion in 2021. Similarly, the protocol for VITdAL-PICU (pediatric ICU) was published in 2017 and will reproduce the VITdAL trial in a pediatric population [33]. In this trial, 67 patients should be recruited to evaluate the feasibility of conducting a larger trial. In addition, the VIOLET (Vitamin D to Improve Outcomes by Leveraging Early Treatment) study is a phase III RCT aimed at evaluating the effects of high-dose vitamin D_3 in reducing mortality in patients with vitamin D deficiency (i.e., 25 [OH]D <20 ng/mL) at risk for acute respiratory distress syndrome.

Current recommendations and recent meta-analysis

Based on the two trials by Amrein et al. [27,28], the Canadian Clinical Practice Guidelines published in 2015 concluded that there are insufficient data to make a recommendation regarding vitamin D supplementation in the critically ill [34]. More recently, the guidelines from the American Society of Parenteral and Enteral Nutrition and the Society of Critical Care Medicine only suggested vitamin D supplementation along with other vitamins and trace elements in obese patients with a previous history of bariatric surgery. In 2018, the European Society for Clinical Nutrition and Metabolism has suggested that in critically ill patients with low plasma levels of vitamin D defined as 25(OH)D <12.5 ng/mL, a high dose of vitamin D_3 equal to 500 000 IU as a single dose should be administered within a week after admission (grade of recommendation: B).

To date, the VITdAL-ICU trial has been the only RCT powered to evaluate clinical outcomes [27], but several smaller trials also reported some interesting data [25,26,28,29,35]. Despite the various strategies of administration across the trials, including doses, route of supplementation, and the chemical form of vitamin D administered, a recent systematic review and meta-analysis aggregated the six RCTs (N = 695 patients) published so far. In this study, the authors were unable to show any effect on mortality (RR, 0.84; 95% C,I 0.66–1.06; $P = 0.14$), including in the subgroup of severely deficient ICU patients. Other clinical outcomes such as hospital and ICU LOS, infectious complications, and duration of mechanical ventilation also were unchanged [30], although statistical imprecision may be explained by the sparse number of RCTs. In 2017, a meta-analysis by Putzu et al. demonstrated reduced mortality after vitamin D supplementation (OR, 0.70; 95% CI, 0.50–0.98; $P = 0.04$) [31]. The difference between the two meta-analyses resides in the inclusion criteria, as Putzu et al. included a positive RCT conducted in 30 patients with cystic fibrosis, in which the authors had found an improvement in mortality with vitamin D therapy [36].

Safety and recommended dietary allowance

The recommended dietary allowance (RDA) of vitamin D is 600 IU for adults <70 y of age and corresponds to the daily dose maximizing bone health and muscle function. However, the daily dose of vitamin D associated with non-skeletal health benefits has not been definitively determined. When >70 y of age, the RDA is 800 IU. Nonetheless, a daily dose of ≥1500 to 2000 IU may be needed to increase 25(OH)D levels to >30 ng/mL [2].

In enteral nutrition (EN), 200 IU is present in about 1 L of EN formulas, whereas in ICU patients on parenteral nutrition (PN), commonly used multivitamin products for adults have a 5 μg/unit dose [37]. In ICU patients, a single dose of 540 000 IU of vitamin D_3 by enteral route has been demonstrated to be able to normalize 25(OH)D levels in critically ill patients [27], although doses as low as 60 000 IU, administered twice over the first week after ICU admission, have been able to significantly improve 25(OH)D concentration [6]. Adverse effects owing to vitamin D toxicity include hyperkalcemia, which generally occurs when 25(OH)D concentration is >160 to 200 ng/mL. The upper limit of intake is 2000 IU/d, although toxicity occurs only when daily intakes are in the range of 40 000 IU.

Conclusion

It is hard not to consider, when treating ICU patients, the increased mortality in the general population when vitamin D levels are <28 ng/mL. Nonetheless, current strategies of supplementing vitamin D do not seem beneficial unless patients are severely deficient, as proposed by the VITdAL-ICU trial [27]. Many different supplementation strategies have been tried and many functional serum markers have been studied, but the pharmacokinetic profile remain scarcely understood. These issues should be elucidated by currently recruiting large RCTs, including the VITDALIZE and the VIOLET studies.

References

[1] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
[2] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911–30.
[3] 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;96:53–8.
[4] 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:R47.
[5] Dickerson RN, Van Cleve JR, Swanson JM, Maish 3rd GO, Minard G, Croce MA, et al. Vitamin D deficiency in critically ill patients with traumatic injuries. Burns Trauma 2016;4:28.
[6] Mata-Granados JM, Vargas-Vasserot J, Ferreiro-Vera C, Luque de Castro MD, Pavon RG, Quesada Gomez 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;121:452–5.
[7] Amrein K, Venkatesh B. Vitamin D and the critically ill patient. Curr Opin Clin Nutr Metab Care 2012;15:188–93.
[8] Christopher KB. Vitamin D and critical illness outcomes. Curr Opin Crit Care 2016;22:332–8.
[9] Lasky-Su J, Dahlin A, Litonjua AA, Rogers AJ, McGeachie MJ, Baron RM, et al. Metabolome alterations in severe critical illness and vitamin D status. Crit Care 2017;21:193.
[10] Xu J, Yang J, Chen J, Luo Q, Zhang Q, Zhang H. Vitamin D alleviates lipopolysaccharideinduced acute lung injury via regulation of the reninangiotensin system. Mol Med Rep 2017;16:7432–8.
[11] Cameron LK, Lei K, Smith S, Doyle NL, Doyle JF, Flynn K, et al. Vitamin D levels in critically ill patients with acute kidney injury: a protocol for a prospective cohort study (VID-AKI). BMJ Open 2017;7:e016486.
[12] Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. Am J Clin Nutr 2012;95:91–100.
[13] Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamaki H, et al. An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. Am J Clin Nutr 2007;86:714–7.
[14] Camargo Jr CA, Ganmaa D, Sidbury R, Erdenedelger K, Radnaakhand N, Khandsuren B. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. J Allergy Clin Immunol 2014;134:831–5. e1.
[15] Moromizato T, Litonjua AA, Braun AB, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically ill. Crit Care Med 2014;42:97–107.
[16] Amrein K, Quraishi SA, Litonjua AA, Gibbons FK, Pieber TR, Camargo Jr CA, et al. Evidence for a U-shaped relationship between prehospital vitamin D status and mortality: a cohort study. J Clin Endocrinol Metab 2014;99:1461–9.
[17] Mayr U, Fahrenkrog-Petersen L, Batres-Baires G, Rasch S, Herner A, Schmid RM, et al. Vitamin D deficiency is highly prevalent in critically ill patients and a risk factor for mortality: a prospective observational study comparing noncirrhotic patients and patients with cirrhosis. J Intensive Care Med 2018:88506661 8803844.
[18] Atalan HK, Gucyetmez B. Serum vitamin D level at ICU admission and mortality. Turk J Anaesthesiol Reanim 2017;45:193–6.

[19] Kose I, Zincircioglu C, Ozkarakas H, Cakmak M, Ersan G, Kuzucu L, et al. Low levels of vitamin D are associated with nosocomial infections but not with short-term mortality in critically ill patients. Turk J Med Sci 2018;48:324–31.
[20] Yadav S, Joshi P, Dahiya U, Baidya DK, Goswami R, Guleria R, et al. Admission vitamin D status does not predict outcome of critically ill patients on mechanical ventilation: an observational pilot study. Indian J Anaesth 2018;62:47–52.
[21] Vassiliou AG, Jahaj E, Mastora Z, Stagaki E, Orfanos SE, Kotanidou A. Serum admission 25-hydroxyvitamin D levels and outcomes in initially non-septic critically-ill patients. Shock 2018;50:511–8.
[22] Otero TMN, Canales C, Yeh DD, Elsayes A, Belcher DM, Quraishi SA. Vitamin D status is associated with development of hospital-acquired pressure injuries in critically ill surgical patients [Epub ahead of print]. Nutr Clin Pract 2018.
[23] Brook K, Otero TMN, Yeh DD, Canales C, Belcher D, Quraishi SA. Admission 25-Hydroxyvitamin D levels are associated with functional status at time of discharge from intensive care unit in critically ill surgical patients [Epub ahead of print]. Nutr Clin Pract 2018.
[24] Gomes TLN, Fernandes RC, Vieira LL, Schincaglia RM, Mota JF, Nóbrega MS, et al. Low vitamin D at ICU admission is associated with cancer, infections, acute respiratory insufficiency and liver failure [Epub ahead of print]. Nutrition 2018.
[25] 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;190:533–41.
[26] Nair P, Venkatesh B, Lee P, Kerr S, Hoechter DJ, Dimeski G, et al. A randomized study of a single dose of intramuscular cholecalciferol in critically ill adults. Crit Care Med 2015;43:2313–20.
[27] 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;312:1520–30.
[28] 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:R104.
[29] Quraishi SA, De Pascale G, Needleman JS, Nakazawa H, Kaneki M, Bajwa EK, et al. Effect of cholecalciferol supplementation on vitamin D status and cathelicidin levels in sepsis: a randomized, placebo-controlled trial. Crit Care Med 2015;43:1928–37.
[30] Langlois PL, Szwec C, D'Aragon F, Heyland DK, Manzanares W. Vitamin D supplementation in the critically ill: a systematic review and meta-analysis. Clin Nutr 2018;37:1238–46.
[31] Putzu A, Belletti A, Cassina T, Clivio S, Monti G, Zangrillo A, et al. Vitamin D and outcomes in adult critically ill patients. A systematic review and meta-analysis of randomized trials. J Crit Care 2016;38:109–14.
[32] Parekh D, Dancer RCA, Scott A, D'Souza VK, Howells PA, Mahida RY, et al. Vitamin D to prevent lung injury following esophagectomy—a randomized, placebo-controlled trial. Crit Care Med 2018;46:e1128–35.
[33] McNally D, Amrein K, O'Hearn K, Fergusson D, Geier P, Henderson M, et al. Study protocol for a phase II dose evaluation randomized controlled trial of cholecalciferol in critically ill children with vitamin D deficiency (VITdAL-PICU study). Pilot Feasibility Stud 2017;3:70.
[34] Critical Care Nutrition. Canadian clinical practice guidelines, 2015. Available at: https://www.criticalcarenutrition.com/docs/CPGs2015/12.02015.pdf. [Accessed 18 December 2018].
[35] Han JE, Jones JL, Tangpricha V, Brown MA, Brown LA, Hao L, et al. High dose vitamin D administration in ventilated intensive care unit patients: a pilot double blind randomized controlled trial. J Clin Transl Endocrinol 2016;4:59–65.
[36] Grossmann RE, Zughaier SM, Kumari M, Seydafkan S, Lyles RH, Liu S, et al. Pilot study of vitamin D supplementation in adults with cystic fibrosis pulmonary exacerbation: a randomized, controlled trial. Dermatoendocrinol 2012;4:191–7.
[37] Sriram K, Lonchyna VA. Micronutrient supplementation in adult nutrition therapy: practical considerations. JPEN J Parenter Enteral Nutr 2009;33:548–62.