Vitamin D in the ICU: anything new under the sun?

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ABSTRACT

The recent recognition of the myriad roles of vitamin D beyond those of bone health and calcium homoeostasis has resulted in a large body of clinical studies demonstrating an association between vitamin D deficiency and a number of adverse health outcomes. While these studies in chronic disease states have shown a strong association between vitamin D deficiency and poor outcomes, they have been unable to demonstrate cause and effect.

Several studies to date have demonstrated a high prevalence of vitamin D deficiency in critically ill patients, and some of these have shown an association with poor outcomes. It is possible that low vitamin D levels may contribute to the acute multiorgan dysfunction seen in critical illness by similar mechanisms to those seen in chronic conditions.

In this commentary, we briefly review the physiology of vitamin D, examine the evidence for association of hypovitaminosis with poor outcome in both ambulatory and intensive care unit patients, and debate the role of routine vitamin D supplementation in the ICU.

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Traditionally, the key role of vitamin D is considered to be in the maintenance of skeletal health. However over the past decade, data from biochemical, molecular genetic studies as well as clinical trials indicate that vitamin D has a much wider range of effects than previously understood.[1] These non-traditional, pleiotropic functions relate to the discovery that numerous extraskeletal cells possess a vitamin D receptor (VDR) as well as a tissue form of 1-α-hydroxylase (CYP27B1). This tissue form of the enzyme activates 25-hydroxyvitamin D (25-OHD) to 1,25-dihydroxyvitamin D ($1,25\text{-}[OH]_2D$; calcitriol) at the local level, which is responsible for its pleiotropic actions. These include inhibiting cellular proliferation, inhibiting angiogenesis, stimulating insulin production, inhibiting renin production and modulating immune function.[1,2] The effects are so profound that it has been likened to the next generation of statins.[3]

Studies have demonstrated that low vitamin D levels are consequently associated with clinical conditions such as hypertension, cardiovascular disease, diabetes, some infections, cancers and autoimmune diseases, schizophrenia and others.[4-10] This knowledge has captured the interest of intensivists as it is possible that low vitamin D levels, by similar mechanisms, may contribute to the acute, multiorgan dysfunction and nosocomial infections seen in the intensive care unit.[11]

Vitamin D physiology

There are three forms of vitamin D: vitamin D_1 (combination of ergocalciferol and lumisterol), vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). The major source of vitamin D is cutaneous synthesis through the effects of the ultraviolet light in sunlight on the skin. Keratinocytes contain 7-dehydrocholesterol, which on exposure to ultraviolet B light is converted to cholecalciferol. This then undergoes a two-step hydroxylation, first in the liver to 25-OHD, and subsequently in the kidney to $1,25\text{-}(OH)_2D$. Formation of $1,25\text{-}(OH)_2D$ from 25-OHD is under both endocrine and paracrine regulation by parathyroid hormone (PTH) (Figure 1). In addition to its classic location in the kidneys, the activating enzyme, 1-α-hydroxylase, is found in almost all cells. Renal 1-α-hydroxylase activation may be important for circulating $1,25\text{-}(OH)_2D$ levels; but locally, $1,25\text{-}(OH)_2D$ formed by tissue 1-α-hydroxylase is critical in mediating the pleiotropic actions of vitamin D. Circulating vitamin D sufficiency is required for both endocrine and paracrine arms of the PTH–vitamin D axis to function effectively. Only 0.03% of 25-OHD is free; about 88% is bound to vitamin D-binding protein and the remainder to albumin. Serum $1,25\text{-}(OH)_2D$ is tightly regulated by PTH, serum calcium and fibroblast growth factor-23. The contemporary Western diet provides only a minor source (< 10%) of vitamin D.[11]

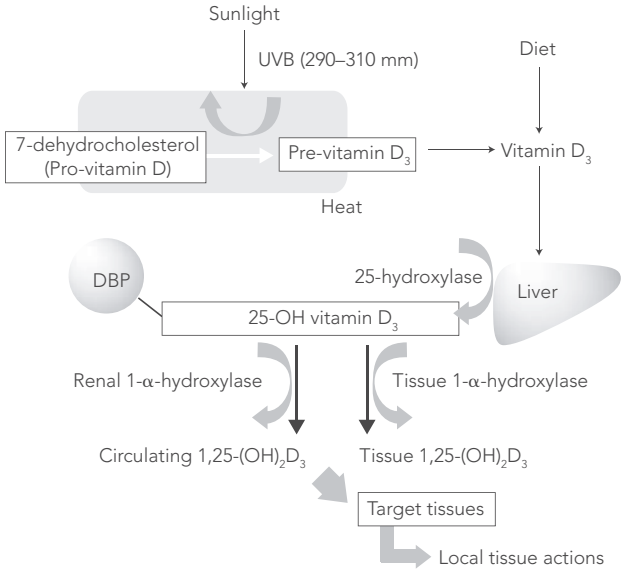
Mechanism of pleiotropic actions

VDRs are present in a number of extraskeletal tissues (Table 1). Vitamin D regulates gene expression through binding with these VDRs and the heterodimeric complexes formed interact with specific DNA sequences within target genes resulting in either activation or repression of transcription.[12]

The actions of vitamin D can be categorised into three general effects:[2]

- Regulation of hormone secretion:
  - inhibits the synthesis and secretion of PTH and prevents parathyroid gland proliferation;
  - stimulates insulin secretion by a mechanism that is not completely clear;

Figure 1. Schematic diagram illustrating synthesis of active vitamin D_3 by sequential hydroxylation in the liver, kidneys and local tissues



Reproduced with kind permission from Springer Science+Business Media: Lee et al.[11] 1,25-$(OH)_2D_3$ = 1,25-dihydroxyvitamin D_3. DBP = vitamin D-binding protein. OH = hydroxy. UVB = ultraviolet B light. Target tissues obtain 1,25-$(OH)_2D_3$ from either a circulating pool formed in the kidneys or locally from tissue 1-α-hydroxylation.

Table 1. Examples of widespread distribution of vitamin D receptors in the human body[12]

System	Tissue
Endocrine	Parathyroid gland, β cells in pancreas
Cardiovascular	Vascular and cardiac muscle cells
Musculoskeletal	Osteoblasts, chondrocytes, striated muscle
Gastrointestinal	Oesophagus, stomach, intestine
Hepatic	Liver parenchymal cells
Renal	Tubules, juxtaglomerular apparatus (renin)
Reproductive	Testis, ovary, uterus
Immune	T and B cells, thymus, bone marrow
Respiratory	Alveolar membrane
Central nervous system	Brain neurones

  - stimulates fibroblast growth factor-23 production, predominantly by osteoblasts and osteocytes.
- Regulation of immune function:
  - adaptive immunity: production of cytokines and immunoglobulins by T and B lymphocytes, respectively. Overall, vitamin D exerts an inhibitory action on the adaptive immune system, which appears to be beneficial in autoimmune disease;
  - innate immunity: activation of toll-like receptors in leukocytes, which leads to the induction of antimicrobial peptides (predominantly cathelicidin) that kill the organism. Lack of substrate 25-OHD or VDRs blunts the ability of these cells to produce cathelicidin.[13,14]
- Regulation of cellular proliferation and differentiation: vitamin D may reduce the risk of cancer by stimulating the expression of cell cycle inhibitors p21 and p27, and of cell adhesion molecules.[2]

Assessment of vitamin D status and interpretation of levels

Serum vitamin D status is assessed using 25-OHD levels, despite 1,25-$(OH)_2D$ being the active form of the vitamin. This is because 25-OHD is stable, plentiful and has a half-life of about 3 weeks, making it the most suitable indicator of vitamin D status. In contrast, the half-life of 1,25-$(OH)_2D$ is only a few hours. Moreover, renal 1-α-hydroxylase can be driven hard enough by the secondary hyperparathyroidism that develops with calcium and vitamin D deficiency, to produce normal or even high levels of calcitriol. However, this does not correct calcium malabsorption from the intestine, which appears to require both calcitriol and 25-OHD. Furthermore, calcitriol produced at tissue level, which is responsible for the non-skeletal functions of vitamin D, cannot be measured clinically.[15-17]

To assess adequacy of vitamin D status, investigators have considered a number of factors. One definition of optimal vitamin D status is the 25-OHD level that maximally suppresses PTH secretion. Another is the 25-OHD level at which there is no incremental increase in 1,25-$(OH)_2D$ level, because it is adequate to meet demand. Yet another is the 25-OHD level that results in maximal intestinal calcium absorption.[18] While these approaches have their shortcomings, all suggest that optimal levels range between 50 and 75 nmol/L. The currently recommended target serum level for 25-OHD by the United States Institute of Medicine is 50–125 nmol/L.[19] In practice, levels > 50 nmol/L are considered sufficient, while levels of 25–50 nmol/L and < 25 nmol/L are considered to be insufficient and deficient, respectively.[18]

Prevalence of vitamin D deficiency in critical illness

Despite abundant natural sunlight in Australia, a high prevalence of vitamin D deficiency has been noted, ranging from 67% to 86% in at-risk groups: elderly, institutionalised or dark-skinned people, veiled women and people admiited to geriatric hospital.[20-23] There also appears to be a significant prevalence of mild vitamin D deficiency, observed in over 20% of healthy, younger adults, particularly during winter in the southern latitudes of Australia.[24]

Table 2. Association of vitamin D levels with outcomes in ambulatory patients

Author	Study design	Outcome	Main findings
Ginde et al[31]	Prospective observational	All-cause mortality	Risk of death 45% lower if 25-OHD > 100 nmol/L compared with < 25 nmol/L
Dobnig et al[32]	Prospective cohort	Cardiovascular mortality	Lowest mortality in highest vitamin D quartile; HR, 0.45 (95% CI, 0.32–0.64)
Yin et al[33]	Meta-analysis	Colon cancer	Reduced risk by 40% for each 50 nmol/L increase in vitamin D
Chen et al[34]	Meta-analysis	Breast cancer	Lower risk in highest quartile of vitamin D; OR, 0.55 (95% CI, 0.38–0.80)
Munger et al[35]	Case–control	Multiple sclerosis	Lowest risk in group with highest vitamin D levels; OR, 0.59 (95% CI, 0.36–0.97)
Brehm et al[36]	Cross-sectional	Allergy and asthma	Low vitamin D levels associated with higher IgE, eosinophil count and asthma-related hospitalisation
Ginde et al[37]	Prospective observational	Infection	Vitamin D < 25 nmol/L more likely to have URTI in all four seasons; stronger association if asthma or COPD
Plotnikoff et al[38]	Descriptive	Musculoskeletal pain	93% with pain had vitamin D < 50 nmol/L
Melamed et al[39]	Prospective cohort	Renal disease	Greater risk with lower vitamin D in African–American patients
Bischoff-Ferrari et al[40]	Prospective cohort	Bone density	Vitamin D levels related to hip BMD in patients > 20 years old

25-OHD = 25-hydroxyvitamin D. BMD = bone mineral density. COPD = chronic obstructive pulmonary disease. HR = hazards ratio. IgE = immunoglobulin E. OR = odds ratio. URTI = upper respiratory tract infection.

In 2009, an initial dedicated evaluation of vitamin D in critically ill patients was conducted in Australia, which revealed a previously underrecognised high prevalence of vitamin D deficiency in ICU. Only 7% of patients had sufficient levels and predicted mortality was three times higher in patients with deficient levels.[25] Several other studies have reported a high prevalence of vitamin D insufficiency/deficiency ranging from 38% to 100% in critically ill patients.[26-30] The reported prevalence is about 50% higher than in patients in general medical wards.

Evidence for association of hypovitaminosis D with poor outcome in non-critically ill ambulatory patients

There is considerable epidemiological data from large population studies linking vitamin D deficiency to all-cause mortality, sudden cardiac death, hypertension, breast and colorectal cancer, falls and type 1 diabetes. Some of these data are shown in Table 2.

A recent meta-analysis of 14 prospective cohort studies showed that for "highest compared with lowest" categories of 25-OHD, the relative risk of mortality was 0.71 (95% CI, 0.50–0.91).[41]

Despite compelling observational data, data from randomised controlled trials (RCTs) of vitamin D replacement in these conditions are sparse and less conclusive.

A meta-analysis of 18 RCTs of vitamin D supplementation in older women reported a 7% lower risk of death in those supplemented.[42] However, two large Women's Health Initiative RCTs of vitamin D and calcium supplementation showed no significant effect on the risk of colorectal cancer[43] or breast cancer.[44]

On the other hand, RCTs on vitamin D supplementation have shown a significant reduction in falls and fractures, as well as benefits in depression and fibromyalgia.[45-47]

At this stage, the enthusiasm for supplementation with a hormone, albeit with a low risk–benefit ratio, should be tempered with the fact that several gaps in knowledge still remain.

Trials in critically ill patients

Several studies, especially in recent years, have confirmed the very high prevalence of vitamin D insufficiency and deficiency in critically ill patients around the world. Some of these have observed associations with adverse clinical outcomes in this patient group. Table 3 summarises the studies performed in the ICU setting.

Implications for ICU patients

A causative role for vitamin D in relation to these adverse outcomes, however, is not proven. Low vitamin D levels may be purely an association with more severely ill patients with multiple comorbidities. Despite several observational studies, to date there are no interventional trials to investigate the impact of vitamin D supplementation. Without such trials it is not possible to recommend routinely supplementing critically ill patients with vitamin D.[56] Previous studies of correcting endocrine perturbations in critical illness using growth hormone replacement,

Table 3. Vitamin D studies in the critically ill population

Author	Year	Study design	No. of patients	Types of patients	Main aims	Main results
van den Berghe et al[48]	2003	Observational interventional	22	ICU LOS > 10 days	Role of vit D in bone turnover of critical illness	All patients were vit D deficient and not corrected with currently recommended oral dose (200–500 IU)
Lee et al[25]	2009	Observational	42	Referral ICU population	Prevalence and association with outcomes	93% prevalence, correlated with calcium and SAPS II score
Jeng et al[49]	2009	Observational	49	Sepsis v non-sepsis v controls	Comparison of vit D, DBP and LL-37 level.	Vit D and LL-37 lower than controls; DBP lower in sepsis; vit D and LL-37 positively correlated
Lucidarme et al[27]	2010	Observational	106	Admissions in warm months	Incidence and risk factors for low vitamin D in ICU	79% prevalence; predictors of severe deficiency were spring admission, low albumin and high SAPS II
Mata-Granados et al[26]	2010	Observational interventional	33	ICU patients v healthy blood donors	Vitamin D status and response to supplements	96.7% prevalence in critically ill, 62% in controls, corrected with supplementation.
McKinney et al[28]	2010	Retrospective	136	Veterans in ICU	Association with low levels and poor outcomes	Vit D sufficient patients had shorter ICU stay and risk of death
Krishnan et al[50]	2010	Observational	19	Undergoing CPB	Effect of acute fluid loading on vit D levels	25-hydroxy and 1,25-hydroxy vit D levels lowered which took 24 hours to recover
Amrein et al[51]	2011	Pilot RCT	25	Vit D < 50 nmol/L, ICU > 48 hours	Effect of high-dose oral vit D	Corrected vit D deficiency within 48 hours in most patients, without adverse effects
Braun et al[29]	2011	Retrospective	2399	Medical and surgical ICU	Prediction of outcome based on admission vit D level	Low pre-admission vit D levels predicted mortality and blood culture positivity
Cecchi et al[30]	2011	Observational	170	Sepsis v trauma	vit D levels & outcomes in sepsis	Significantly lower vit D levels in sepsis v trauma patients, but no relationship with outcome
Venkatesh et al[52]	2011	Observational	14	ICU LOS > 2 days	Variability of vit D and PTH levels in a 24-hour period	Random vit D levels may not reflect 24-hour profile
Venkatram et al[53]	2011	Retrospective	437	Medical ICU	Vit D levels and mortality in medical ICU	Increased hospital mortality in vit D deficient patients
Flynn et al[54]	2012	Observational	66	Surgical ICU	Vit D level and outcome in surgical ICU	Increased LOS, organ dysfunction and infection rates if vit D < 50 nmol/L
Matthews et al[55]	2012	Observational	191	Surgical ICU	Relationship with VAP	Increased VAP incidence, LOS and costs with vit D deficiency

CPB = cardiopulmonary bypass. DBP = vitamin D-binding protein. LL-37 = cathelicidin. LOS = length of stay. RCT = randomised controlled trial. SAPS II = Simplified Acute Physiology Score. VAP = ventilator-associated pneumonia. Vit D = vitamin D.

steroid supplementation and intensive insulin therapy suggest that caution is required before implementation of hormone replacement strategies.[57-59]

Population studies in ambulatory patients suggest that vitamin D doses that were previously used (200–500 units/day) are inadequate for the non-skeletal actions of vitamin D and larger doses (300 000–600 000 units/day) may be required.[60] Large prospective RCTs are needed to ascertain safety and efficacy, and, importantly, to test whether a supplemented 25-OHD status improves outcome in an intensive care setting.

Competing interests

No relevant disclosures.

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