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

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. 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 1α-hydroxylase (CYP27B1). This tissue form of the enzyme activates 25-hydroxyvitamin D (25-OHD) to 1,25-dihydroxyvitamin D (1,25-[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. The effects are so profound that it has been likened to the next generation of statins.

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. 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 seen in the intensive care unit.

Vitamin D physiology

There are three forms of vitamin D: vitamin D1 (combination of ergocalciferol and lumisterol), vitamin D2 (ergocalciferol) and vitamin D3 (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-(OH)2D. Formation of 1,25-(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, 1α-hydroxylase, is found in almost all cells. Renal 1α-hydroxylase activation may be important for circulating 1,25-(OH)2D levels; but locally, 1,25-(OH)2D formed by tissue 1α-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-(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.

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.

The actions of vitamin D can be categorised into three general effects:
- 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;
- Other biological actions of vitamin D include the following:
  - stimulation of intestinal calcium absorption;
  - inhibition of cellular proliferation;
  - inhibition of angiogenesis;
  - stimulation of insulin production;
  - inhibition of renin production;
  - modulation of immune function.

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.
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;

• 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 admitted 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
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 cancer43 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,
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.

### Author details

**Priya Nair**, Senior Staff Specialist

**Bala Venkatesh**, Professor of Intensive Care, and Deputy Director

1 Intensive Care Unit, St Vincent’s Hospital, Sydney, NSW, Australia. 
2 Intensive Care Unit, Princess Alexandra Hospital, Brisbane, QLD, Australia. 
3 Wesley Hospital, Brisbane, QLD, Australia. 

**Correspondence**: pnair@stvincents.com.au

---

### Table 3. Vitamin D studies in the critically ill population

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Types of patients</th>
<th>Main aims</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>van den Berghe et al48</td>
<td>2003</td>
<td>Observational interventional</td>
<td>22</td>
<td>ICU LOS &gt; 10 days</td>
<td>Role of vit D in bone turnover of critical illness</td>
<td>All patients were vit D deficient and not corrected with currently recommended oral dose (200–500 IU)</td>
</tr>
<tr>
<td>Lee et al25</td>
<td>2009</td>
<td>Observational</td>
<td>42</td>
<td>Referral ICU population</td>
<td>Prevalence and association with outcomes</td>
<td>93% prevalence, correlated with calcium and SAPS II score</td>
</tr>
<tr>
<td>Jeng et al49</td>
<td>2009</td>
<td>Observational</td>
<td>49</td>
<td>Sepsis v non-sepsis v controls</td>
<td>Comparison of vit D, DBP and LL-37 level.</td>
<td>Vit D and LL-37 lower than controls; DBP lower in sepsis; vit D and LL-37 positively correlated</td>
</tr>
<tr>
<td>Lucidarme et al27</td>
<td>2010</td>
<td>Observational</td>
<td>106</td>
<td>Admissions in warm months</td>
<td>Incidence and risk factors for low vitamin D in ICU</td>
<td>79% prevalence; predictors of severe deficiency were spring admission, low albumin and high SAPS II</td>
</tr>
<tr>
<td>Mata-Granados et al26</td>
<td>2010</td>
<td>Observational interventional</td>
<td>33</td>
<td>ICU patients v healthy blood donors</td>
<td>Vitamin D status and response to supplements</td>
<td>96.7% prevalence in critically ill, 62% in controls, corrected with supplementation.</td>
</tr>
<tr>
<td>McKinney et al28</td>
<td>2010</td>
<td>Retrospective</td>
<td>136</td>
<td>Veterans in ICU</td>
<td>Association with low levels and poor outcomes</td>
<td>Vit D sufficient patients had shorter ICU stay and risk of death</td>
</tr>
<tr>
<td>Krishnan et al50</td>
<td>2010</td>
<td>Observational</td>
<td>19</td>
<td>Undergoing CPB</td>
<td>Effect of acute fluid loading on vit D levels</td>
<td>25-hydroxy and 1,25-hydroxy vit D levels lowered which took 24 hours to recover</td>
</tr>
<tr>
<td>Amrein et al51</td>
<td>2011</td>
<td>Pilot RCT</td>
<td>25</td>
<td>Vit D &lt; 50 nmol/L, ICU &gt; 48 hours</td>
<td>Effect of high-dose oral vit D</td>
<td>Corrected vit D deficiency within 48 hours in most patients, without adverse effects</td>
</tr>
<tr>
<td>Braun et al29</td>
<td>2011</td>
<td>Retrospective</td>
<td>2399</td>
<td>Medical and surgical ICU</td>
<td>Prediction of outcome based on admission vit D level</td>
<td>Low pre-admission vit D levels predicted mortality and blood culture positivity</td>
</tr>
<tr>
<td>Cecchi et al30</td>
<td>2011</td>
<td>Observational</td>
<td>170</td>
<td>Sepsis v trauma</td>
<td>Vit D levels &amp; outcomes in sepsis</td>
<td>Significantly lower vit D levels in sepsis v trauma patients, but no relationship with outcome</td>
</tr>
<tr>
<td>Venkatesh et al52</td>
<td>2011</td>
<td>Observational</td>
<td>14</td>
<td>ICU LOS &gt; 2 days</td>
<td>Variability of vit D and PTH levels in a 24-hour period</td>
<td>Random vit D levels may not reflect 24-hour profile</td>
</tr>
<tr>
<td>Venkatram et al53</td>
<td>2011</td>
<td>Retrospective</td>
<td>437</td>
<td>Medical ICU</td>
<td>Vit D levels and mortality in medical ICU</td>
<td>Increased hospital mortality in vit D deficient patients</td>
</tr>
<tr>
<td>Flynn et al54</td>
<td>2012</td>
<td>Observational</td>
<td>66</td>
<td>Surgical ICU</td>
<td>Vit D level and outcome in surgical ICU</td>
<td>Increased LOS, organ dysfunction and infection rates if vit D &lt; 50 nmol/L</td>
</tr>
<tr>
<td>Matthews et al55</td>
<td>2012</td>
<td>Observational</td>
<td>191</td>
<td>Surgical ICU</td>
<td>Relationship with VAP</td>
<td>Increased VAP incidence, LOS and costs with vit D deficiency</td>
</tr>
</tbody>
</table>

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.
References

2 Bikle D. Non-classic actions of vitamin D. J Clin Endocrinol Metab 2009; 94: 26-34.
14 Youssef DA, Miller CW, El-Abbassi AM, et al. Antimicrobial implica-
22 Inderjeeth CA, Nicklason F, Al-Lahham Y, et al. Vitamin D deficiency and secondary hyperparathyroidism: clinical and biochemical asso-
37 Ginde AA, Mansbach JM, Camargo CA Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infec-
41 Zittermann A, iodice S, Pilz S, et al. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospec-


