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# Vitamin D deficiency in ICU patients

A review on the role of vitamin D in a well-defined setting of critically ill patients: patients undergoing cardiac surgery and organ transplantation, and the potential benefit of vitamin D supplementation.

hospital length of stay, was similar between groups, but mortality was substantially and significantly lower in patients with severe vitamin D deficiency.

In this short review, we will focus on the role of vitamin D in a well-defined setting of critically ill patients: patients undergoing cardiac surgery and organ transplantation. We will highlight the rationale for the potential benefit of vitamin D supplementation and briefly discuss the ongoing large intervention trials in the ICU setting.

**▶▶ vitamin D deficiency is associated with greater illness severity, morbidity, and mortality in both paediatric and adult critically ill patients ▶▶**

## Vitamin D and acute illness/mortality/immune function

Vitamin D is a pre-hormone acting via its metabolite 1,25-dihydroxy vitamin D<sub>3</sub>, with direct and indirect effects in most human tissues and cell types. The best studied actions of vitamin D include the modulation of bone and muscle metabolism, and a number of non-classical and pleiotropic wide-ranging biological effects. Several studies have recognised how vitamin D deficiency is associated with greater illness severity, morbidity, and mortality in both paediatric and adult critically ill patients. Vitamin D works through endocrine, autocrine, and paracrine actions that activate a variety of rapid effects, but also a number of signaling pathways and human epigenomic responses that probably need

days to become effective. Given its actions, vitamin D has the potential to represent an independent, modifiable risk factor amendable to rapid normalisation through loading dose supplementation.

Vitamin D<sub>3</sub> (cholecalciferol), is absorbed from food sources or produced by the skin in the presence of sunlight. After being metabolised by the liver into 25-hydroxy-vitamin D [25(OH)D] and further converted to its biologically active form 1,25-dihydroxy-vitamin-D [1,25(OH)<sub>2</sub>D] by the kidneys within 2-3 days, it binds with high affinity to the vitamin D receptor (VDR) in many organs. Besides its well-known effects on calcium homeostasis and bone health, vitamin D shows immunomodulating (Sassi et al. 2018), and organ protective properties (Amrein et al. 2018). Moreover, ICU patients, especially patients undergoing cardiopulmonary bypass surgery and transplant patients appear to be at high risk for developing osteoporosis and fragility fractures in the long term, and vitamin D deficiency is an important risk factor.

Vitamin D deficiency - generally defined as 25(OH)D serum levels lower than 20 ng/mL (equals 50 nmol/l) - is reported in 40 to 70% of all ICU patients (Amrein et al. 2018), and is even more common after transplant surgery with a prevalence of 50 to 90% (Thiem et al. 2013). It is associated with an increased risk of mortality, organ dysfunction, infections, prolonged ICU and hospital stay as well as increased duration of mechanical ventilation in several observational trials (Amrein et al. 2014a; de Haan et al. 2014).

While VITDAL-ICU, the largest prospective interventional trial including 480 critically ill patients failed to show an overall beneficial effect of high dose (540.000 IU oral cholecalciferol) supplementation in the general

**V**itamin D research has experienced a true hype in all fields of medicine in the last decades. In critical illness, this increased interest has only started 10 years ago. The high prevalence of vitamin D deficiency in critically ill patients and the rationale for a modulating role of vitamin D in acute illness but also long-term outcomes is certainly intriguing. However, vitamin D is no panacea, so it is not surprising that even large studies like the recent VITAL trial were unable to demonstrate an effect of vitamin D in a relatively healthy and largely vitamin D replete population (Manson et al. 2019).

So far, the Austrian VITDAL-ICU trial was the largest RCT (n= 480) to test the hypothesis that high dose cholecalciferol supplementation in a mixed population of critically ill patients with vitamin D deficiency may rapidly restore plasma vitamin D concentrations and improve clinical outcomes. The primary endpoint,

ICU population, a significantly reduced risk of 28-day mortality was observed in a subgroup of patients with severe 25(OH)D deficit <12 ng/mL (equals 30 nmol/l) (Amrein et al. 2014b).

Patients receiving prehospital vitamin D supplementation have significantly shorter ICU stay, fewer days of mechanical ventilation and lower rates of mortality (Leclair et al. 2019), supporting the importance of the availability of biologically active vitamin D at the time of acute illness.

### Vitamin D and cardiac surgery

Within cardiac surgery patients, 40 to 80% demonstrate 25(OH)D levels lower than 20ng/mL preoperatively and experience a significant intraoperative decrease in biologically active vitamin D serum levels (Ney et al. 2018). Preoperative malnutrition, poor general health, limited sunlight exposure, and preexisting liver and kidney dysfunction are primary causes of vitamin D deficiency in this cohort. Open heart surgery is associated with alarming complication rates (15-20%) and mortality rates of about 3-4% (Herman et al. 2013). The significant systemic inflammation can cause severe organ injury and dysfunction resulting in serious life-threatening complications. The setting of inflammation additionally leads to a downregulation of 25(OH)D and 1,25(OH)2D by the enzyme 24-hydroxylase and a reduction of the vitamin D binding protein with as a result lower serum levels (Al Tarrah et al. 2018). Vitamin D is involved in the regulation of the immune system, modulates the endothelial function and has an effect on arterial stiffness. The exact mechanism of action is still being investigated. However, 1,25-dihydroxy-vitamin-D triggers an upregulation of antibacterial peptides such as cathelicidin by macrophages and monocytes, which in turn is capable of eradicating infectious cells. Active immune cells can locally convert 25(OH)D into the active form of vitamin D in order to provide immunoprotective properties. Furthermore, 1,25(OH)2D activates several anti-inflammatory mediators (e.g. IL-4 and IL-10) and inhibits pro-inflammatory cytokines such as interferon, interleukin 2 and 6 and tumour necrosis factor (Sassi et al. 2018; Ramos-Martinez et al. 2018). These cardioprotective properties have been shown to improve clinical outcome after cardiac surgery.

Several observational studies showed that low preoperative 1,25(OH)2D levels are associated with an increased risk of organ dysfunctions and infections in cardiac surgery patients (Ney et al. 2018; Zittermann et al. 2016). In addition, vitamin D deficient cardiac surgery patients showed a significantly higher frequency of postoperative atrial fibrillation and major adverse cardiac and cerebrovascular events. Although some studies show a correlation between low preoperative vitamin D levels and mortality (Zittermann et al. 2013), others were not able to replicate these results (Turan et al. 2013). Since there are many factors influencing mortality rates such as the preoperative health condition, the surgical procedure itself and the cardiopulmonary bypass time, vitamin D's role remains unclear. Even though vitamin D deficiency is extremely prevalent in this patient cohort and supplementation might help to improve clinical outcome after cardiac surgery, no intervention trials have been carried out so far. Future studies are needed to address this issue.



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## Vitamin D and organ transplantation

Several studies have highlighted that lower 25-hydroxyvitamin D levels at ICU admission, also in post-surgical ICU, are associated with prolonged hospitalisation, ICU readmission, and mortality.

Given its wide immunobiological effects, vitamin D has been frequently considered a potential modulating factor after solid organ (and stem cell) transplantation (mainly liver, kidney and lung). The transplantation recipient population is particularly prone to infections, mainly in the early stage after transplantation, due to immunomodulation/chronic immunosuppressive therapy and to long term bone dysfunction.

The reasons for insufficient vitamin D levels in the transplant setting are manifold and comprise limited sunlight exposure and reduced dietary intake of vitamin D containing food as well as liver and kidney dysfunction.

In liver transplantation recipients, osteoporosis has a high prevalence with a large decline in bone mineral density in the first year after transplantation. Vitamin D levels are often very low in liver recipients. Moreover, a negative association between low vitamin D levels and graft function as well as a role of vitamin D in reducing the recurrence of hepatitis C virus infection has been demonstrated. In a recent cohort of Swiss liver recipients, the pre-transplantation vitamin D status was associated with the incidence of infections in the first 6 months.

The modulating effect of vitamin D and the presence of its specific receptor in almost all cells and tissues of the human body, with the preliminary data on low vitamin D status and outcome call for an action in this field to understand if vitamin D is only a “bystander” (just a marker of disease) or if it is a potential modulator of clinical trajectories in this specific setting.

## The future

The two large ongoing vitamin D supplementation trials in general critical illness including thousands of vitamin D deficient patients (NCT03096314 and NCT03188796) will provide more knowledge soon. VIOLET randomised patients with 25hydroxyvitamin D levels below 20 ng/ml “at risk for ARDS” to a single high dose of vitamin D3 (540,000 IU) and evaluated its effect on the primary outcome 90-day-mortality. It was prematurely stopped in 2018, and no results have yet been published.

VITDALIZE is a European multicentre RCT including severely vitamin D deficient patients in the ICU with a 25-hydroxyvitamin D level < 12 ng/ml and randomises patients to a loading dose of vitamin D3 (540,000 IU) followed by 4000 IU daily for 90 days – the primary outcome is 28-day-mortality. Currently, more than 20 sites in Austria (PI: K. Amrein) and Belgium (PI: J.Ch. Preiser) are active and recruitment will continue for the next few years.

In conclusion, vitamin D deficiency is highly prevalent and associated with adverse outcomes worldwide in paediatric and adult critically ill patients. Moreover, it appears reasonable that vitamin D deficiency is an important contributor to adverse outcomes during and following acute illness. If so, vitamin D’s overall effect may be small, but even a tiny effect of an inexpensive treatment, on important clinical outcomes, with a very low rate of side effects, may prove to be a game changer in intensive care some day. ■

## Key points

- Vitamin D has the potential to represent an independent, modifiable risk factor amenable to rapid normalisation through loading dose supplementation.
- Vitamin D deficiency is associated with an increased risk of mortality, organ dysfunction, infections, prolonged ICU and hospital stay as well as increased duration of mechanical ventilation.
- Preoperative malnutrition, poor general health, limited sunlight exposure, and pre-existing liver and kidney dysfunction are primary causes of vitamin D deficiency.
- High dose vitamin D supplementation is safe and cost-effective in critically ill patients.
- Vitamin D shows immunomodulating, organ protective and bone health promoting properties in high risk cardiac surgery and transplant patients

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