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Understanding vitamin D deficiency in intensive care patients

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Introduction

Vitamin D deficiency (VDD) is a well-established cause of musculoskeletal disease. Over the past few decades a growing body of literature has changed our understanding of vitamin D and proposed roles in infectious, immunologic, neurologic, cardiovascular, and respiratory disorders [1]. More recently VDD has been hypothesized as a modifiable risk factor for poor outcome in the hospitalized and specifically the ICU patient [1–3].

Prevalence of vitamin D deficiency and risk factors in intensive care

Circulating 25-hydroxyvitamin D [25(OH)D] is the accepted marker for evaluating vitamin D status. Although some controversy remains, there are generally accepted thresholds for defining vitamin D sufficiency (75 nmol/L), deficiency (50 nmol/L), and severe deficiency (30 nmol/L) [1]. Applying the 50 nmol/L threshold, ICUs worldwide have reported VDD rates ranging from 60 to 100 % [3–6].

Critically ill patients arrive at ICU or become deficient thereafter for many reasons (overview in Fig. 1). Similar to the general population, achieving adequate status through diet is difficult as only a select few foods contain vitamin D (eggs, avocado, fish, fortified milk)—the standard western diet rarely contains more than 150 IU/day. Further, most individuals have one or more genetic or behavioral factors that negatively influence UV photosynthesis of vitamin D (high latitude, sun avoidance, sun screen, skin melanin content, young/old age, clothing, pollution). These problems are amplified for hospitalized patients who often have a number of comorbidities. Besides critical illness itself, therapeutic interventions including surgery, fluids, extracorporeal membrane oxygenation, cardiopulmonary bypass, and plasma exchange may significantly reduce vitamin D levels [7]. Further, ICU patients are at risk for disruption of the vitamin D axis due to hepatic, parathyroid, and renal dysfunction impairing conversion of 25(OH)D to the active hormone, reduced end organ resistance, and—very likely—relatively greater requirements.

Current approach to vitamin D supplementation

Presently, ICU patients either receive no or low-dose vitamin D supplementation (200–800 IU/day) consistent

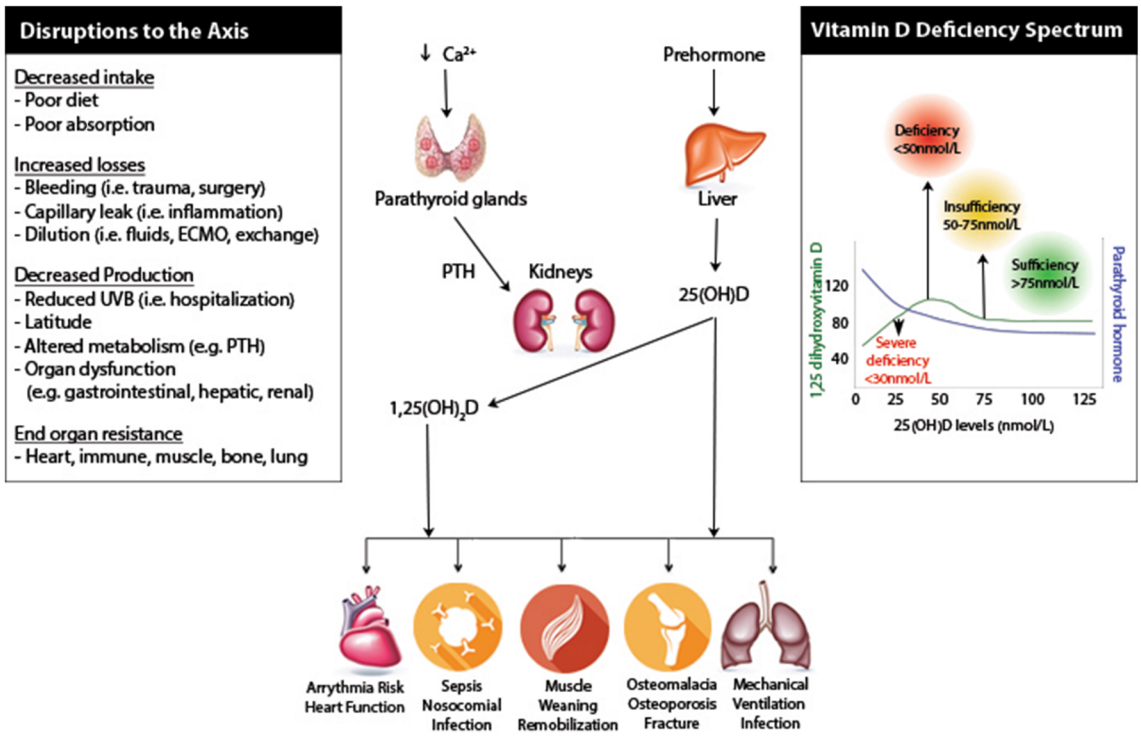

Fig. 1 The vitamin D axis is best understood in the context of hypocalcemia: as serum calcium falls, the parathyroid increases parathyroid hormone (PTH) secretion. Higher blood PTH leads to activation of vitamin D through an inducible renal enzyme, converting serum 25-hydroxyvitamin D [25(OH)D] to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. This active hormone circulates to the bone, gut, and kidneys to restore homeostasis. Importantly, it is now well recognized that many cell types in the body possess the enzymes capable of converting 25(OH)D to its active form for both autocrine or paracrine use. Although thresholds and terminology vary, vitamin D sufficiency is generally accepted as a 25(OH)D level above 75, deficiency as under 50, and severe deficiency below 25 or 30 nmol/L (to convert nmol/L to ng/ml, divide by 2.5). These thresholds are based on biochemical indicators of axis stress and values below which disease predisposition rises. When 25(OH)D falls below 50 nmol/L, maintenance of circulating active hormone 1,25$(OH)_2$D levels requires elevation of serum PTH and increased renal enzyme activity. As 25(OH)D falls below 30 nmol/L, production of active hormone falls and healthy individuals may develop electrolyte disturbances and clinically relevant bone or muscular disease

with recommended minimal intake for the healthy population [8]. It is, however, well established that using such doses, months may be required to replenish vitamin D stores. In hospitalized patients, it may even be impossible to normalize levels [9, 10].

Does vitamin D deficiency matter during critical illness?

Vitamin D is best known for its role in the regulation of calcium levels through well-described gastrointestinal, renal, and bone actions. In addition, the vitamin D receptor has been identified on multiple other organs central to critical illness pathophysiology (Fig. 1). Through these receptors, vitamin D exerts important physiologic functions via both genomic and nongenomic pathways [11]. Supporting basic science research, a growing body of observational data in critically ill and other populations has described associations between VDD and increased illness severity and outcomes, health resource utilization, and mortality [3–5, 12–14].

Evidence from intervention trials

Multiple research groups have recognized the need for alternative supplementation approaches and pilot dosing studies have been completed. At present, only one randomized controlled trial (RCT) has been performed with appropriate power to allow for comment on the clinical efficacy of rapid normalization (VITdAL-ICU). This trial randomized 475 critically ill adults to an initial enteral 540,000 IU cholecalciferol loading dose (followed by monthly 90,000 IU) or placebo doses. Although the trial did not find a difference in the primary endpoint "length of hospital stay" there was a non-significant absolute risk reduction in hospital mortality of 7.0 % in the vitamin D

arm. This absolute difference became larger and statistically significant (−17.5 %, $p = 0.01$) in the predefined subgroup of patients with vitamin D levels below 30 nmol/L at baseline (HR 0.56, 95 % CI 0.35–0.90) [9].

Future directions in research and potential barriers

Demonstrated biological plausibility, consistent findings from observational studies, and early evidence from VITdAL-ICU make a compelling case. Further, the widespread notion of vitamin D as a simple, inexpensive, and safe medication makes it tempting to fast track recommendations for high-dose supplementation. Yet, it is currently not entirely clear if a poor vitamin D status is primarily an indicator of multimorbidity, unhealthy lifestyle and a consequently poor prognosis and the optimal level remains unknown in and out of the ICU. Furthermore, there are potential side effects showing that supraphysiological vitamin D levels (greater than 200 nmol/L) may cause adverse events including hypercalcemia and hypercalciuria. Consequently, we should seek to gain further evidence from large, well-done RCTs.

Yet, researchers intent on undertaking these trials will face a number of challenges. First, there is a lack of equipoise on the 25(OH)D threshold that should be applied to study eligibility. A hurried inspection of VITdAL-ICU would support the 30 nmol/L threshold. However, this would ignore the VITdAL-ICU findings suggesting long-term improvements in physical functioning in patients with baseline levels between 30 and 50 nmol/L. Second, researchers will need to address the delays in reporting of vitamin D levels (potentially weeks) by local laboratories as delay in treatment could significantly reduce the treatment effect. Emerging point-of-care tests could address this problem, but require external validation. Third, there will be debate about the correct vitamin D metabolite(s) and dosing regimen for each. Although the combined safety and cost profile makes enteral cholecalciferol the early favorite, it cannot be overlooked that a substantial proportion of ICU patients have gastrointestinal pathology or critical illness-induced malabsorption. Unfortunately, there is no commercially available high-dose intravenous (IV) form of cholecalciferol and IV calcitriol (active hormone) is both expensive and potentially more dangerous, although a subpopulation of patients may require both metabolites. Finally, as with most "pleiotropic" interventions it will be challenging to select optimal endpoints. Mortality may be the right outcome for a severely ill adult ICU population with very low baseline 25(OH)D levels, but inappropriate in the setting of higher 25(OH)D thresholds or populations less likely to die (i.e., pediatrics).

Conclusion

Both in adult and pediatric ICU populations, a low vitamin D status is very common and associated with excess morbidity and mortality. Although some promising findings from intervention studies exist, the available evidence is insufficient to recommend widespread use of high-dose vitamin D. Therefore, we urgently need large, methodologically sound multicenter RCTs taking into account the barriers outlined above.

Conflicts of interest The authors report no conflict of interest.

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