



EDITORIAL

Vitamin D as a modifiable risk factor in critical illness: questions and answers provided by observational studies^{☆,☆☆}

Vitamina D como um fator de risco modificável em doenças graves: perguntas e respostas de estudos observacionais

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Vitamin D is essential to optimal health. Studies dating back to the early 1900's convincingly demonstrate that a state of vitamin D deficiency, acquired through limited sun exposure and avoidance of vitamin D-rich foods can lead to stunted growth, bone disease, and hypocalcemic seizures. Over the past few decades, a rising body of epidemiological literature has also suggested that vitamin D deficiency predisposes to a wide variety of disease states outside of the musculoskeletal system. For example, vitamin D status has been associated with diseases involving dysregulation of the immune (type I diabetes, cancer), cardiovascular (heart failure, cardiomyopathy), and respiratory systems (bronchiolitis, pneumonia). Strong biological plausibility supporting these epidemiological findings has been provided, including basic science studies showing the presence of vitamin D receptors on a large number of diverse cell types (e.g. white blood cells, myocytes), and animal studies demonstrating disease occurrence in genetically- (vitamin D

receptor knockout) or nutritionally-induced vitamin D deficiency states.

As the pathophysiology of the immune, cardiovascular, respiratory, and renal systems is central to critical illness, it is not surprising that clinicians and researchers have also hypothesized that vitamin D may be a modifiable risk factor in the intensive care setting. Since the initial NEJM publication in 2009 by Lee et al.,¹ there have been dozens of adult epidemiological studies on this subject, and the overwhelming majority reported high vitamin D deficiency rates and statistical relationships with illness severity. In the adult realm, interventional studies are underway, with the publication of two pilot phase II studies evaluating rapid restoration regimens^{2,3} and the initiation of a large randomized controlled trial.⁴

In comparison, the importance of vitamin D in pediatric critical illness is significantly less studied, and the publication by Rey et al. in this issue⁵ adds to this emerging body of literature. Notwithstanding the publication by Rey et al. the pediatric literature on vitamin D in critically ill children was summarized in a recent review.⁶ The initial pediatric studies addressing this question were published in late 2012.^{7,8} Including the publication by Rey et al., there are now two studies on mixed medical/surgical populations, two on isolated medical populations, and two on isolated cardiac surgery populations.^{5,7–11} Although some variability was observed, all studies report clinically significant vitamin D deficiency prevalence rates (30% to 80%). The four

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studies involving post-operative cardiac surgery patients reported statistically significant relationships between low 25-hydroxyvitamin D (25OHD) and greater illness severity. The picture is less clear for the studies on pediatric intensive care unit populations, with only two of the four studies documenting such a statistically significant association. Although the most recent study by Rey et al. did not present any statistically significant associations, there were some potential trends noted, and the study was at risk for type II error given the small sample size and unadjusted analysis.

Does the optimization of vitamin D status prevent or speed recovery from pediatric critical illness? Multiple research groups, most recently Rey et al., have performed the standard initial studies used to answer research questions of this variety. An evaluation of the available studies demonstrates that, regardless of geography, many critically ill children are vitamin D deficient. This observation would appear to present an opportunity. The missing information is whether and to what extent the natural history of disease is modified by raising vitamin D levels. Observational studies on nutrients and hormones are often used to predict the potential magnitude of effect by comparing illness course in groups of patients with different levels. Regardless of whether the results show the desired associations, clinicians and researchers struggle to interpret and compare the findings from both singular and groups of observational studies. This is due to small sample size, patient heterogeneity (within and between studies), measurement error, confounding factors, outcome selection, statistical analysis, and reporting biases. In addition to the standard problems associated with PICU studies of this nature, there are other problems specific to vitamin D that further complicates the issue. First, although recognized as the appropriate marker of vitamin D status in most populations, 25OHD levels may not accurately reflect body stores in critically ill patients (those with hypoparathyroidism, renal dysfunction, interstitial leak of binding proteins, fluid shifts, dialysis). It has been suggested that blood concentrations of the active vitamin D hormone might better reflect vitamin D axis function, a question that will require further studies, which will also suffer from the abovementioned problems. Second, association studies intended to evaluate and demonstrate that higher vitamin D levels prevent illness or speed recovery suffer from a lack of patients with blood 25OHD levels that represent the target. Stated differently, it is not possible to estimate the benefits of a 25OHD level of 100 nmol/L when few of the study participants achieve this target.

What advice should be given regarding vitamin D supplementation to clinicians who care for patients who are either at risk for critical illness or are critically ill? For now, it would appear prudent to provide pre-illness supplementation in a range known to safely maintain 25OHD at 100 nmol/L (1,000 to 2,000 IU/day).^{12,13} There are specific populations that deserve special attention and may require higher supplementation doses to achieve desired vitamin D status (patients with renal dysfunction, malabsorption syndromes, anti-seizure medications, cardiopulmonary bypass).^{14,15} With good compliance, a daily intake in the 1,000 to 4,000 IU range for two to three months should achieve target vitamin D levels. An alternative approach is required to optimize vitamin D status in the actively critically ill patients who are vitamin D deficient. What is clear

is that daily administration of low dose vitamin supplementation (400 to 4,000 IU/day) will not restore levels in a beneficial time frame. Instead, clinicians will need to consider loading doses (or stoss therapy) ranging from 50,000 to 600,000 IU, depending on starting level and weight.^{16–18} Given evidence (albeit largely from case reports/series) that high doses may cause hypercalcemia, hypercalciuria, or nephrocalcinosis, vitamin D loading doses cannot be recommended in critically ill children without clinical trial data.^{19,20} As such, the next steps in this emerging field are patience (results of the adult stoss therapy randomized clinical trials) and completion of smaller phase II dose-evaluation studies in children.

Conflicts of interest

The author declares no conflicts of interest.

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