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Journal Title: Critical Care
Volume: Volume 16, Number 4
Publisher: BioMed Central | 2012, Pages 316-316
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1186/cc11252
Permanent URL: <http://pid.emory.edu/ark:/25593/fksh2>

Final published version: <http://ccforum.com/content/16/4/316>

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Accessed January 26, 2020 10:04 PM EST

VIEWPOINT

Vitamin D in sepsis: from basic science to clinical impact

Jordan A Kempker^{*1}, Vin Tangpricha², Thomas R Ziegler³ and Greg S Martin¹

Abstract

The growing basic and clinical investigations into the extraskeletal effects of vitamin D have revealed roles in the functioning of the immune system, generating interesting questions about this nutrient's connections to sepsis. This article briefly reviews the current science of the function of vitamin D in the immune system as well as the emerging clinical literature regarding its associations with respiratory infections, sepsis, and critical illness. Finally, we offer views on the potential future directions for research in the field by outlining potential relevant scenarios and outcomes.

With the discovery of the vitamin D receptor (VDR) and 25-hydroxyvitamin D-1 α -hydroxylase in many extraskeletal tissues and the vitamin D response element in over 900 genes, scientists are beginning to uncover that vitamin D, a secosteroid hormone, may have roles in the optimal functioning of many organ systems and chronic illnesses [1-5]. The interest in vitamin D status was exemplified by the 2011 Institute of Medicine (IOM) report establishing a minimum serum 25-hydroxyvitamin D (25(OH)D) concentration of 20 ng/mL as the optimal level for skeletal health in the US [6] and the Endocrine Society recommendation of a concentration of at least 30 ng/mL for optimal health benefits [2]. The scope of this problem certainly affects the subset of patients with critical illness and sepsis, and recent reports show that 79% to 98% of intensive care unit (ICU) patients are vitamin D-insufficient [7-9].

Vitamin D and immune function

One of the most promising extraskeletal roles of vitamin D for patients with sepsis is in the functioning of the

immune system (Table 1). This was initially indicated by the discovery of VDRs in nearly all types of immune cells [10], spanning the body's innate and adaptive immune responses to pathogens. Further studies have revealed that vitamin D modulates immune responses to the pro-inflammatory bacterial endotoxin (lipopolysaccharide) *in vitro* and in rodent models of sepsis [11-16] and shown evidence that vitamin D is involved in the monocyte response to *Candida albicans* [17].

In addition to affecting the humoral response to sepsis, vitamin D acts in the local tissue response to infection [18] and is integral to the production of antimicrobial peptides (AMPs) [19,20]. A landmark study by Liu and colleagues [21] in 2006 revealed the critical role of vitamin D in the macrophage response to *Mycobacterium tuberculosis* via the AMP cathelicidin. The active fragment of cathelicidin is LL-37, which has been shown to be produced by phagocytic leukocytes, mucosal epithelium, and keratinocytes and to be present in mucosal secretions and plasma [22]. Its immune functions include direct bactericidal activity as well as disruption of *Pseudomonas aeruginosa* biofilms, promotion of phagocytosis and reactive oxygen species, and chemotaxis of other immune cells to sites of infection [22]. These properties have been demonstrated to have efficacy in *in vitro* studies of human airway and bladder pathogens [23,24].

Complementing the basic science research, clinical research has examined the role of vitamin D in the prevention and control of respiratory infections, the most common source of sepsis in the US [25]. The clinical literature has a wide array of study designs, selected populations, and interventions and has demonstrated mixed results. Whereas observational studies among adults have revealed an association between low vitamin D and the incidence of respiratory infections [26,27], clinical trials have not produced strong results [28,29]. Among children, observational studies examining the relationship between low vitamin D and respiratory infections have also shown varied results [3,30-34], yet in two intervention trials, vitamin D reduced rates of recurrence of respiratory infections at 3 months [35] and decreased the incidence of influenza A infection [36]. The

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Table 1. Basic science research of the role of vitamin D in infection

Immune response to bacteria

- Modulates cytokine profiles and hemostatic parameters in response to bacterial endotoxin (lipopolysaccharide) in rodent models and *in vitro* experiments of human monocytes and endothelial cells
- Involved in the macrophage response to *Mycobacterium tuberculosis*, bronchial cell response to *Pseudomonas aeruginosa*, and bladder cell response to *Escherichia coli* via the antimicrobial peptide cathelicidin

Immune response to fungi

- Modulates cytokine profiles in human monocytes exposed to *Candida albicans*

Immune response to virus

- Decreases production of inflammatory proteins without increase in viral replication in tracheobronchial cells infected with respiratory syncytial virus

Lessons from these early trials include the dosing to ensure vitamin D repletion, the need for larger sample sizes or higher-risk populations that may show larger effect sizes, and recognition of relevant short- and long-term endpoints. Given that a recent query of intervention trials on 'vitamin D' and 'infection' on ClinicalTrials.gov yielded 67 results, the picture of the role of vitamin D in infection will likely become clearer in the near future.

Vitamin D in sepsis and critical illness

Although infection is a necessary cause for sepsis, it is still uncertain whether vitamin D will have a clinically detectable effect on this common pathway with such a variety of infective antecedents that leave patients *in extremis*. Furthermore, the potential effects of vitamin D on other physiologic systems make it difficult to isolate its relationship to sepsis in the critically ill. In this population, the research examining the associations between vitamin D and hypocalcemia, bone resorption, insulin resistance, pulmonary function, and cardiovascular events may yet reveal therapeutic effects in critically ill and septic patients [4,5,37-42]. Although examining these topics is beyond the scope of this paper, they are important effects to consider in understanding the literature on vitamin D and sepsis.

Much of the current clinical science regarding vitamin D and sepsis is nested within the larger studies of critically ill patients. Studies examining vitamin D insufficiency and sepsis within critical illness have had mixed designs and results. One retrospective study of 136 veterans admitted to the ICU demonstrated a significantly increased survival rate (69% versus 44%) among those with serum 25(OH)D concentrations of greater than 20 ng/mL [8]. A multicenter retrospective observational study of 2,399 medical and surgical ICU patients with serum 25(OH)D levels drawn within the year prior to admission showed an increase in all-cause mortality among vitamin D-insufficient and -deficient groups [43]. An analysis of the patients in this source population with a 25(OH)D concentration drawn within 7 days of ICU admission revealed similar results [44]. In either analysis, the presence of sepsis did not modify the association

between vitamin D and mortality, but in the first study, a significant association between low serum 25(OH)D concentrations and an increase in blood culture positivity was found [43]. A retrospective study of 437 ICU patients showed similar findings, with a significant relationship between in-hospital mortality and vitamin D deficiency that was not influenced by any admission category, including sepsis [45]. In regard to the surgical ICU, a recent study of 66 patients found trends toward higher rates of infection and sepsis in those with a serum 25(OH)D concentration of less than 20 ng/mL [46].

In addition to this research in the larger population of the critically ill, investigation specifically examining vitamin D and sepsis has begun. However, this work is still in its early phases. All of the published literature in this area is observational but has revealed some interesting findings. In a prospective study of 92 patients with severe sepsis and septic shock in comparison with trauma patients, vitamin D was a predictor of mortality in the univariate analysis, yet the relationship became insignificant in the multivariate analysis [47]. Another study followed 81 patients suspected of an infection in the emergency department and found that patients with serum 25(OH)D concentrations of less than 30 ng/mL were more likely at enrollment and at 24 hours to have more occurrences of severe sepsis and organ dysfunction [48]. Our group found that, in ICU patients, serum LL-37 levels positively correlated with 25(OH)D concentrations and that vitamin D-binding protein (VDBP) was decreased in patients with sepsis in comparison with those without sepsis [11]. This raises new questions about the role of VDBP in mediating vitamin D responses in the ICU. Furthermore, it demonstrates how translational research designs can create a reciprocal dialogue between the basic and clinical sciences and may help drive research in this area.

In summary, the results of the clinical science of vitamin D and sepsis are mixed, yet it would be simplistic to dismiss this field of research on such grounds. The failure of vitamin D to produce effects in the current observational literature may be a result of study design and insufficient power to reveal a mortality difference.

Table 2. Future research questions in vitamin D and sepsis

Vitamin D and the burden of sepsis in the community

- What serum 25(OH)D concentration is optimal for immune function?
- Can vitamin D supplementation reduce the incidence of infection and progression to sepsis?
- Is vitamin D a causal factor of racial health disparities in sepsis?
- Is vitamin D a causal factor of the seasonal variations in infection and sepsis?

Vitamin D in the health-care setting

- Is serum 25(OH)D concentration a reliable measure of vitamin D in critical illness?
- Can acute vitamin D repletion alter the progression of sepsis and severity of organ dysfunction?
- Can vitamin D repletion reduce the incidence of hospital-acquired infections?
- What is a safe dosing schedule for rapid vitamin D repletion and maintenance therapy in hospitalized patients?

25(OH)D, 25 hydroxyvitamin D.

Although the pluripotency of vitamin D sparks our interest for a treatment affecting sepsis mortality, it may be unrealistic to power a study to show such a difference. The results of the Cochrane review by Bjelakovic and colleagues [49], who demonstrated a vitamin D-induced 0.6% absolute reduction on all-cause mortality in the general population, would be challenging to translate to critically ill patients with sepsis. Even if the median follow-up time were disregarded, a clinical trial to detect a 0.6% mortality difference would require a sample size of over 100,000, even in low-mortality ICUs. Allocation of this enormous amount of resources for such a small effect size is not justifiable.

Trial design is not the only important challenge in studying vitamin D and sepsis. There are several issues regarding the measurement and interpretation of serum 25(OH)D in this population. Although the IOM report defined a 25(OH)D concentration of 20 ng/mL for skeletal health, we still do not know what level may be optimal for immune function [6]. Furthermore, it is still uncertain whether serum 25(OH)D is an appropriate measure for the effects of vitamin D on the immune system. With the abilities of immune cells to activate and concentrate vitamin D, it is possible that low serum concentrations may be a signal of an activated immune system in the acute phase rather than a risk factor for impaired immunity. Even if serum measures were indicative of risk, another issue is the reliability of serum 25(OH)D concentrations in septic patients receiving fluid resuscitation. A study of cardiac surgery patients demonstrated that the hemodilutional effects of fluid resuscitation can decrease serum 25(OH)D concentration by up to 35% [50]. All of these issues present significant challenges that must be accounted for with intelligent trial design and data analysis.

Future directions

The challenges in the field of vitamin D and sepsis may seem daunting, but the basic and clinical data show

promise. An interesting connection for future research is the association between vitamin D and the potential role of statins in treating sepsis [51]. Certain statins have been associated with increasing vitamin D, and although a recent meta-analysis did not support their role in preventing infections, there is still potential for the use of statins during sepsis [51-53]. Furthermore, although it may be difficult to show mortality benefits in sepsis with vitamin D, work can proceed in investigating the facets of the relationship which are suggested by the basic sciences. Here, it seems that the data are strongest when showing that vitamin D has the potential to prevent infections, whether community- or hospital-acquired, and to diminish the severity of sepsis and consequent organ dysfunction. These realms open a wide array of clinical research questions (Table 2) that need to be addressed if we are to be successful in revealing the truth. In the planning of future research, it may be useful to conceptualize and test the potential roles of vitamin D as a 'primary prevention,' 'acute intervention,' and 'secondary prevention.'

In the first hypothetical role, as a 'primary prevention,' vitamin D may serve to help prevent infections and diminish the severity of sepsis in the community. This question lends itself to observational investigation, following cohorts prospectively when they come to medical attention or retrospectively in large administrative databases. Some interesting questions here are the potential causal role of vitamin D in the associations between African-American race and winter season on rates of infections and sepsis. In regard to race, studies have shown that, when compared with Caucasians, African-Americans are more likely to develop sepsis [54,55], develop more infections [56], and have higher rates of organ dysfunction with sepsis [57]. Although vitamin D status was not included in these studies, African-Americans tend to have lower serum 25(OH)D concentrations than Caucasians [58], and this is explained in part by the fact that melanin absorbs the

ultraviolet B light that produces vitamin D in skin [59]. Furthermore, in the US, there is a seasonal variation of respiratory infections and sepsis – namely higher incidences in the winter and the lower ones in the fall – which is more pronounced in the Northeast [60]. These patterns parallel the annual variations in serum 25(OH)D concentrations, which peak in the fall and reach the lowest point after the winter and are also less pronounced closer to the equator [61]. Other than the confounders of age, sex, sun exposure, and socioeconomic status, an associated factor in these relationships may be obesity. Given the positive relationship between obesity and vitamin D deficiency as well as a concern for increased infection and inflammation in the obese, this may be a potential confounding or interacting factor in the relationship between vitamin D and sepsis [62]. These are interesting speculations that require the intensivist to expand the scope of research beyond the ICU to cohorts within the general population or those admitted to the hospital.

The second hypothetical role of vitamin D, as an ‘acute pharmacologic intervention,’ is more familiar territory for intensivist investigators, yet research should still proceed with caution. Here, pilot dose-finding and clinical outcome data are needed to inform the design of rigorous intervention trials should pilot studies show potential benefits of vitamin D supplementation in ICU patients. In regard to potential toxicities of vitamin D, there are not much data. Reports suggest frank toxicity with hypercalcemia at serum concentrations of greater than 200 ng/mL; however, long-term studies of all-cause mortality suggest that vitamin D may show a reverse J-shaped curve in which mortality increases at concentrations of greater than 30 to 48 ng/mL [6]. For acute treatment, small trials of treatment in the ICU have shown that two doses of 60,000 IU or a single dose of 540,000 IU of oral vitamin D₃ can rapidly and safely normalize serum 25(OH) concentrations [63,64]. Aside from the issue of toxicities, the therapeutic effects of vitamin D are most likely subtle and small and should be sought accordingly. Its low toxicity does not need a large beneficial effect for a therapeutic index to justify use. However, its potential pleiotropic effects in the critically ill population at large make identifying specific primary outcomes challenging. Potential sepsis-specific outcomes include progression and severity of sepsis and organ dysfunction. AMP concentrations in blood, bronchial fluid, and peripheral monocytes may be used as targets for identifying the mechanism of these effects. As growing basic science data clarify the relationships with the cardiovascular, respiratory, and endocrine systems, it may become scientifically valid to include other important endpoints for critical illness, such as ventilator and ICU days, lung injury scores, and vasopressor and insulin

requirements. Consideration should also be given to using combined endpoints that group together the multiple potential measurable effects it may have on sepsis and the dysfunction of various organ systems. These outcomes are relatively specific to the ICU and the time a patient spends there, yet in designing these trials, investigators should keep in mind endpoints that encompass the third potential therapeutic role of vitamin D, as a ‘secondary prevention.’

Repletion of vitamin D, in its capacity as a ‘secondary prevention,’ on admission and maintenance therapy over time may serve to protect patients against hospital-acquired infections and recurrence of sepsis in vulnerable populations. This hypothetical role is similar to the role aspirin plays in acute coronary syndromes, for which patients who present with an index case are given a loading dose and then maintained on prolonged therapy to prevent recurrent events. Our group is currently collecting data on a medical ICU cohort to examine the relationship between plasma 25(OH)D concentration at ICU admission and the risk for hospital-acquired infections. We are also performing a pilot comparative effectiveness trial of various high-dose vitamin D₃ regimens in surgical ICU patients (ClinicalTrials.gov identifier NCT01372995).

Although basic science research suggests that vitamin D may have integral roles in the optimal functioning of the immune system, it is not clear whether correction of vitamin D depletion or optimization of vitamin D status or both are efficacious as an adjunctive therapy in the prevention or treatment of infection, particularly in critical care. However, known effects on multiple organ systems, including the immune system, suggest that research on the effects of vitamin D treatment may be promising. Emerging studies showing small or no effects of vitamin D treatment on mortality suggest that dose responses need to be carefully evaluated and clinical trials should be rigorous in order to evaluate the potential role of this nutrient in critical illness.

Abbreviations

25(OH)D, 25-hydroxyvitamin D; AMP, antimicrobial peptide; ICU, intensive care unit; IOM, Institute of Medicine; VDBP, vitamin D-binding protein; VDR, vitamin D receptor.

Acknowledgments

This work was supported in part by National Institutes of Health grants T32 AA013528 (JAK), R21 HL110044, K23AR054334 (VT), K24 RR023356 (TRZ), U54 RR-024380, and P50 AA-013757 (GSM) and the Atlanta Clinical and Translational Science Institute (UL1 RR025008).

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Published: 19 July 2012

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doi:10.1186/cc11252

Cite this article as: Kempker JA, et al.: Vitamin D in sepsis: from basic science to clinical impact. *Critical Care* 2012, **16**:316.