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Vitamin D and sepsis

An emerging relationship

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Abbreviations: 1 α -OHase, 25-hydroxyvitamin D 1 α -hydroxylase; 1,25(OH)₂D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ALRI, acute lower respiratory infections; AMP, antimicrobial peptides; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; LPS, lipopolysaccharide; NHANES, National Health and Nutrition Examination Survey; PAMP, pathogen-associated molecular patterns; PMN, peripheral blood mononuclear cells; PRR, pathogen-recognition receptors; SOFA, Sepsis-related Organ Failure Assessment; TLR, Toll-like receptors; URI, upper respiratory infections; VDR, vitamin D receptors; UVB, ultraviolet-B; VDRE, vitamin D response element

Vitamin D insufficiency and sepsis are both highly prevalent worldwide problems and this article reviews the emerging science that is defining the intersections of these conditions. The importance of vitamin D's role in skeletal health has long been understood but recent evidence is beginning to highlight its role in the functioning of other physiologic systems of the body. Basic science data reveal its integral role in local immune responses to pathogens and the systemic inflammatory pathways of sepsis. Furthermore, clinical scientists have found associations with respiratory infections, critical illness and sepsis but the causal relationship and its clinical impact have yet to be clearly defined. The article ends with speculations on the connections between racial disparities and seasonal differences in sepsis and vitamin D insufficiency.

and its prevalence. In 2011, the Institute of Medicine issued a publication establishing a serum 25-hydroxyvitamin D (25(OH)D) concentration of 20ng/mL as an optimal concentration for skeletal health for the US population.⁷ In the same year, the Endocrine Society recommended a serum 25(OH)D concentration of at least 30 ng/mL for optimal health benefits.³ Using the Endocrine Society's target, 40–100% of US elderly individuals in the community are vitamin D insufficient along with an estimated 1 billion people in the world.⁸

The developing science around vitamin D has begun to reveal potential links between its deficiency and sepsis. The connections between these conditions are still in the early phases of discovery. This review will discuss the various basic and clinical research studies that are examining this relationship, covering the data from experimental models of infection and sepsis to the clinical data on respiratory infections and critical illness.

Introduction

The importance of vitamin D on bone health and calcium homeostasis has long been understood. However, scientists are beginning to uncover that this steroid hormone has important roles in the optimal functioning of many organ systems. Vitamin D receptors and 25-hydroxyvitamin D-1 α -hydroxylase (1 α -OHase) have been discovered in many extraskeletal tissues and the vitamin D response element (VDRE) found in over 900 genes.¹ Furthermore, recent epidemiologic and clinical trials have suggested that optimal vitamin D status may be protective against several chronic illnesses, including risk of systemic infection, cardiovascular disease, lung disease and diabetes.^{2–6}

Highlighting the importance of the recent discoveries of vitamin D's pleiotropic effects on human health, numerous recent publications have explored the definition of vitamin D deficiency

Vitamin D and the Immune System

A vital role for vitamin D in the human system was initially indicated by the discovery of vitamin D receptors (VDR) in nearly all types of immune cells, including activated CD4⁺ and CD8⁺ T cells, B cells, neutrophils, macrophages and dendritic cells.⁹ These cells span the body's innate and adaptive immune responses to pathogens. The relationship being uncovered by scientists is complex, yet the underlying theme seems to be one of modulating the adaptive immune response while promoting innate immunity.¹⁰ In regards to adaptive immunity, vitamin D affects the proliferation and differentiation of B and T cells and modulates immunoglobulin production¹⁰ with one study showing suppression of antibody response to pneumococcal antigens in mice.¹¹ While these effects may have important roles in autoimmunity, it is not yet clear whether they will have a beneficial role in infection or sepsis. In contrast, vitamin D's promotional effects on innate immunity have been more clearly elucidated at this time and will be the focus in this review.

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The innate immune system acts to rapidly identify invading organisms and respond with humoral and cellular defense mechanisms to contain, neutralize and remove offending pathogens. These pathogens are identified by highly conserved pathogen-associated molecular patterns (PAMP) that bind to pathogen-recognition receptors (PRR) on immune cells. The cells that participate in these innate immune responses include neutrophils and monocytes as well as epithelial cells that not only provide barrier function but also have anti-pathogen activity. As discussed below (Table 1), vitamin D is a key component in several of the pathways of this system.^{9,12}

Vitamin D and the Sepsis Cascade

Monocytes play important roles in the innate immune system as antigen presenting cells as well as in phagocytosis. Human monocytes recognize some PAMPs by a family of transmembrane molecules, the Toll-Like Receptors (TLRs). TLR4 specifically recognizes and binds to lipopolysaccharide (LPS), a substance produced by gram-negative bacteria and a potent stimulator of the sepsis inflammatory cascade. Sadeghi et al. demonstrated that human monocytes stimulated with LPS and treated with 1,25-dihydroxyvitamin D (1,25(OH)₂D), showed dose-dependent decreases in TLR2 and TLR4 synthesis, with an increase in CD14, a TLR co-stimulatory molecule.¹³ They further found that 1,25(OH)₂D decreased TNF α and tissue factor, both end products of LPS activation and important inflammatory molecules in sepsis.¹³ These effects were reversed with the introduction of a VDR antagonist, reinforcing a key role of vitamin D in this signaling mechanism.¹³

Further studies have revealed a role for vitamin D in the endothelial response to LPS. In sepsis, LPS activates endothelial cells to produce transcription factor NF κ B, the pro-inflammatory cytokines IL-6 and IL-8, and the chemokine, RANTES. In a study by Equils et al., human endothelial cells treated with 1,25(OH)₂D then stimulated with LPS, showed significant inhibition of these molecules when compared with cells only

exposed to LPS.¹⁴ These findings may suggest that vitamin D acts to modulate the pro-inflammatory endothelial response to LPS.

Over the past two decades, these intriguing vitamin D-dependent cellular responses to LPS have also been studied in rat and mouse models of sepsis. Horiuchi et al. exposed mice simultaneously to intraperitoneal LPS and oral 1,25(OH)₂D. Compared with controls, mice that received vitamin D had less expression of the inflammatory molecule, iTXB₂, and a decrease in mortality.¹⁵ In 2001, Asakura et al. demonstrated that compared with low-molecular weight heparin, treatment with oral 1,25(OH)₂D had equal or improved effects on hemostatic parameters and markers of organ dysfunction in rats infused with LPS.¹⁶ In 2007, Moller et al. performed placebo controlled trials of treatment with 1,25(OH)₂D in three different rat models of sepsis showing varied results.¹⁷ While the different models of sepsis and vitamin D treatments in these experiments make them difficult to compare, when combined with the in vitro data they suggest that vitamin D has important modulatory effects on the innate immune response to LPS-induced sepsis.

While LPS is an important molecule in gram-negative sepsis, vitamin D may also have a role in the sepsis cascade induced by fungal organisms. A study by Khoo et al. treated peripheral blood mononuclear cells (PBMC) with 1,25(OH)₂D and exposed them to *C. albicans*. The PBMCs demonstrated significant dose-dependent decreases in production of pro-inflammatory cytokines with a decrease in expression of the PRRs that recognize *C. albicans*.¹⁸

Vitamin D and Local Immune Defense

Vitamin D's effects on the innate immune system encompass not only the modulation of the systemic inflammatory response but also the local control of pathogens. In vitro studies have shown that 50,000–90,000 IU/ml of vitamin D₃ inhibited growth or killed strains of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, and *Escherichia coli*.¹⁹ Another study of tracheobronchial epithelial cells infected with respiratory syncytial

Table 1. Basic science studies of vitamin D and the innate immune response. Summary of basic science data showing vitamin D's effects in cell and animal models of infection and sepsis

| Year | Author | Design | Results |
|------|-------------------------------|--|--|
| 1991 | Horiuchi et al. ¹⁵ | Mice given intraperitoneal LPS and 1,25D | Decrease iTXB ₂ and mortality |
| 2001 | Asakura et al. ¹⁶ | Rats given LPS infusion with 1,25D or LMWH | Equal or improved hemostatic parameters and markers of organ dysfunction |
| 2006 | Sadeghi et al. ¹³ | Human monocytes given LPS and 1,25D | Dose-dependent decrease in TLR2, TLR4, TNF α , TF and increase in CD14 |
| 2006 | Equils et al. ¹⁴ | Human endothelial cells given LPS and 1,25D | Inhibition of IL-6, IL-8, RANTES and NF κ B |
| 2007 | Moller et al. ¹⁷ | Rats with Cecal Ligation given 1,25D | Decreased thrombocytopenia and total bilirubin rise |
| | | Rats given IV or intraperitoneal LPS and 1,25D | Increased creatinine |
| 2009 | Yim et al. ²⁴ | Human bronchial epithelial cells given 1,25D | Increased LL-37 and reduced growth of <i>P. aeruginosa</i> and <i>B. bronchioseptica</i> |
| 2010 | Nelson et al. ²¹ | Monocytes from bovine mastitis model | Increased expression of monocyte VDR and 1 α -OHase |
| 2010 | Hertting et al. ²⁵ | Human bladder cells after 3 mo oral 25D in vivo with in vitro <i>E. coli</i> challenge | Increased LL-37 and bactericidal activity |
| 2011 | Khoo et al. ¹⁸ | Human PBMCs exposed to <i>C. albicans</i> and 1,25D in vitro | Dose-dependent decrease in TNF α , IL-6, IL-17, TLR2, TLR4 and mannose receptors |

1,25D, 1,25-dihydroxyvitamin D; 25D, 25-hydroxyvitamin D.

virus showed decreases in inflammatory proteins without increases in viral replication when treated with 1,25(OH)₂D.²⁰ In a model of bovine mastitis, Nelson et al. showed that infiltrating monocytes from infected mammary tissue increased gene expression of VDR and 1 α -OHase.²¹ This lends support to a vitamin D-dependent response of the innate immune system that is triggered by local infection.

Another important component of the innate immune response is the antimicrobial peptides (AMP). These peptides initiate bacterial killing by increasing bacterial cell membrane permeability once inside a phagosome.¹² Studies have revealed vitamin D-dependent steps in this process, demonstrating that the binding of bacterial ligands to monocyte PRRs induces gene expression of the VDR and 1 α -OHase genes.¹² In an autocrine fashion, 1 α -OHase activates 25(OH)D which binds to VDRs and then vitamin D response elements (VDRE) to induce genes for the AMPs, β defensin 4A and hCAP18.¹² The latter molecule is then cleaved to its active form LL-37.

LL-37 in particular has been extensively studied in its role in the vitamin D-dependent pathways of the innate immune system. It is produced by phagocytic leukocytes, mucosal epithelium and keratinocytes, and is present in mucosal secretions and plasma.²² LL-37 has shown in vitro microbicidal activity against important human pathogens including *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Escherichia coli*, *Listeria monocytogenes*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *vancomycin-resistant enterococci*.²³ In addition to direct microbicidal activity, it has demonstrated disruption of *Pseudomonas aeruginosa* biofilms, promotion of phagocytosis and reactive oxygen species, and chemotaxis of other immune cells to sites of infection.²² In one study human bronchial epithelial cells incubated with 1,25(OH)₂D showed increased production of LL-37 and reduced growth of airway pathogens, *Bordetella bronchioseptica* and *Pseudomonas aeruginosa*.²⁴ In another study of human bladder cells challenged with *Escherichia coli*, oral vitamin D pretreatment of subjects increased production of LL-37 and bactericidal activity.²⁵ This effect was neutralized with anti-LL-37 antibodies, highlighting LL-37 as a critical antibacterial component of the vitamin D mediated immune response.²⁵ LL-37 also appears to be linked to vitamin D status in humans as a study by Jeng et al. showed a positive correlation between plasma concentrations of LL-37 and 25(OH)D among patients admitted to the ICU.²⁶

Clinical Research on Vitamin D and Infection

Complementing the basic science research of vitamin D's effects on the innate immune system, clinical trials have examined its role in the prevention and control of human infection (Table 2). The studies have predominantly studied vitamin D's role in respiratory infections, the most common source of sepsis in the United States²⁷ and the results have been mixed.

One of the early observational studies that pointed toward a connection between vitamin D and respiratory infections was a secondary analysis of over 18,000 individuals of the US. National Health and Nutrition Examination Survey (NHANES) III. In

this study, Ginde et al. found an inverse relationship between serum 25(OH)D concentrations and the incidence of upper respiratory infections (URI).²⁸ Vitamin D has since been studied in several clinical trials to characterize its role in respiratory infections. In 2010, Sabetta et al. conducted a prospective cohort study showing that serum 25(OH)D concentrations of 38 ng/mL or greater were associated with a 2-fold decrease in the number of upper respiratory infections.²⁹ In contrast, Laaksi et al.'s randomized trial of vitamin D supplementation (400 IU daily of vitamin D₃) did not show a significant difference in the days absent from work due to URI, although only about 30% of the intervention group achieved a 25(OH)D concentration > 32 ng/mL.³⁰ Also of note, this study did show a significant increase in the number of men remaining healthy throughout the 6-mo study period.³⁰ Another randomized study by Li-Ng et al. revealed that winter month oral vitamin D supplementation (2,000 IU daily of vitamin D₃) did not reduce the incidence, duration or severity of URIs among ambulatory adults.³¹

In addition to these studies on URIs, there have been a number of studies examining the relationship between vitamin D and acute lower respiratory infections (ALRI) in infants and children. Three case-control studies of newborns and children admitted with ALRI showed an association between low vitamin D status and risk of ALRI.³²⁻³⁴ In contrast, two other case-control studies did not reveal an association between vitamin D status and hospitalization for ALRI in children, although one of them showed that it was associated with admission to the ICU.^{35,36} In an intervention trial, Manaseki-Holland et al. showed that a single oral dose of 100,000 IU of vitamin D in children admitted for ALRI reduced rates of recurrence in the subsequent three months, although it did not shorten the duration of the index infection.³⁷ Urashima et al. conducted a randomized trial of vitamin D supplementation (1,200 IU daily of vitamin D₃) in school aged children during the winter and found that supplementation significantly decreased the incidence of influenza A infection, especially among children with predisposing respiratory conditions.³⁸

The varied results of these studies may be methodological with the different study designs, vitamin D treatments, outcome measures and sample sizes. Rather than nullify the findings from the basic sciences, they help direct future research in this area by indicating that vitamin D's effects on infection will likely be small and need large samples sizes and supplementation needs to be adequate and sustained. In translating this research to sepsis it is important to note that most of the above studies do not focus on specific infective pathogens. While respiratory infections are the most common cause of sepsis in the US, gram-positive bacteria are the most common pathogens, followed by gram-negative bacteria with a rise in fungi.³⁹ However, the clinical literature on vitamin D and these organisms is sparse. A case-control study of the NHANES, found an association between low vitamin D and increased nasal colonization with MRSA.⁴⁰ Also a cross-sectional study of veterans with clostridium difficile and staphylococcus aureus infections, showed more hospitalizations and a 4-fold increase in hospital length of stay among those with serum 25(OH)D < 20 ng/mL.⁴¹ Despite the limitations of the

Table 2. Clinical studies of vitamin D and infections: Summary of observational and experimental data on vitamin D's effects in infections

| Year | Author | Design | Sample Size | Results |
|--|---------------------------------------|--|-------------|--|
| Observational Studies | | | | |
| 2009 | Ginde et al. ²⁸ | Case-control study of NHANES III | n = 18,883 | Inverse relationship between 25D levels and incidence of URI |
| 2009 | Wayse et al. ³² | Case-control study of children < 5 y old in India | n = 150 | 25D > 9 ng/mL associated with lower risk of ALRI |
| 2009 | Karatekin et al. ³³ | Case-control study of infants admitted to NICU for ALRI in Turkey | n = 40 | Admission for ALRI associated with lower 25D levels |
| 2009 | Roth et al. ³⁵ | Case-control study of infants 1–25 mo old admitted for ALRI in Alberta | n = 129 | No difference in 25D levels among children admitted for ALRI |
| 2009 | McNally et al. ³⁶ | Case-control study of infants 1–11 mo old admitted for ALRI in Saskatchewan | n = 197 | There was no difference in 25D levels among children admitted for ALRI |
| 2010 | Youssef et al. ⁴¹ | Cross-sectional analysis of veterans with <i>MSSA</i> and <i>C. difficile</i> infections and 25D level within 3 mo | n = 52 | 25D < 20ng/mL associated with increased costs and hospitalization days |
| 2010 | Matheson et al. ⁴⁰ | Case-control study of NHANES 201–2004 | n = 14,639 | 25D < 20 ng/mL associated with increased risk of nasal carriage of MRSA |
| 2010 | Sabetta et al. ²⁹ | Prospective cohort of healthy US adults | n = 198 | 25D > 38 ng/mL associated with 2 fold decrease in URI |
| 2010 | Roth et al. ³⁴ | Case-control study of infants 1–18 mo of age admitted for ALRI in Bangladesh | n = 50 | Admission for ALRI was associated with lower 25D levels |
| Experimental Studies of Patients Given Oral Vitamin D | | | | |
| 2009 | Li-Ng et al. ³¹ | RCT of New York adult volunteers given 2000 IU/day for 12 weeks | n = 162 | No difference in incidence of URIs |
| 2010 | Laaksi et al. ³⁰ | RCT of Finnish men in military training randomized to 6 mo of 400 IU/day | n = 164 | Increased number of men remaining healthy during study but no difference in days missed from duty due to respiratory infections. |
| 2010 | Manaseki-Holland et al. ³⁷ | RCT of children 1–36 mo old admitted to hospital in Kabul for ALRI given 100,000 IU once | n = 453 | Reduced recurrence ALRI at 90 d but no difference duration of index ALRI |
| 2010 | Urashima et al. ³⁸ | RCT of Japanese schoolchildren given 1200 IU/day D over four winter months | n = 334 | Reduced incidence of influenza A |

25D, 25-hydroxyvitamin D; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; RCT, randomized controlled trial.

research on vitamin D and infection, clinical science is still moving forward in exploring its connections with sepsis.

Vitamin D in the Critically Ill

As vitamin D's role in the immune system is beginning to be pieced together through its local and systemic effects on immune responses to pathogens, there has been an interest in its role in critically ill patients (Table 3). While this review will focus on the prevalence of vitamin D insufficiency and its connections with sepsis in the critically ill, it is important to note vitamin D's other potential roles within this population, including patients with severe hypocalcemia, increased bone turnover in prolonged illness and a possible connection with insulin resistance.⁴²⁻⁴⁴

Several studies have revealed a high prevalence of vitamin D insufficiency among the critically ill, although its association with outcomes has been less clear. A single center prospective observational study examined all ICU patients admitted in a spring-summer season and found serum 25(OH)D concentrations < 24 ng/mL in 79%.⁴⁵ Spring admission, low albumin and high Simplified Acute Physiology II score were all independently associated with low serum 25(OH)D concentrations.⁴⁵ They did

not find associations between vitamin D, mortality or hospital-acquired infections in the overall group or in the septic subgroup.⁴⁵ McKinney et al. conducted a retrospective study of 136 veterans admitted to the ICU who had a serum 25(OH)D drawn within a month before or after admission to the ICU. Ninety-eight percent of the veterans had low serum 25(OH)D concentrations.⁴⁶ The study also demonstrated a significantly increased survival rate (69% vs. 44%) among those with serum 25(OH)D concentrations greater than 20 ng/mL.⁴⁶ A retrospective study by Venkatram et al. revealed an association between mortality and vitamin D deficiency (25(OH)D < 20 ng/mL) in 437 patients at a single center ICU.⁴⁷

Other studies have provided more specific data on the relationship between vitamin D and septic patients. Jeng et al. showed that vitamin D insufficiency was present in 100% of critically ill patients with sepsis, 92% of critically ill patients without sepsis and 66.5% in healthy controls.²⁶ A prospective study of 66 surgical ICU patients showed a non-significant trend toward an increased rate of infections and sepsis among the vitamin D deficient (< 20 ng/mL).⁴⁸ Braun et al. conducted two retrospective studies on the same source population investigating this subject. One was a retrospective analysis of 2,399

Table 3. Clinical studies of vitamin D and sepsis: summary of observational data on the links between vitamin D and sepsis among the critically ill

| Year | Authors | Design | Sample Size | Results |
|------|--------------------------------|--|-------------|---|
| 2009 | Jeng et al. ⁴⁶ | Case-control study of patients admitted with or without sepsis compared with non-hospitalized controls in Atlanta | n = 70 | Prevalences of 25D < 30ng/mL: 100% in sepsis, 92% and 66.5% in controls |
| 2010 | Lucidarme et al. ⁴⁵ | Prospective cohort in ICU in France | n = 134 | Seventy-nine percent with 25D < 24 ng/mL, associated with high SAPS II score but not nosocomial infections or mortality |
| 2011 | Cecchi et al. ⁵¹ | Prospective cohort of patients with severe sepsis and septic shock compared with trauma patients in a general ICU in Florence, Italy | n = 170 | Median 25D concentration was lower in septic group and associated with increased mortality only in unadjusted analysis |
| 2011 | McKinney et al. ⁴⁶ | Retrospective cohort of veterans admitted to a Tennessee ICU with a 25D level drawn within the month | n = 136 | Sixty percent with 25D < 30ng/mL, which was associated to mortality |
| 2011 | Flynn et al. ⁴⁸ | Prospective observational cohort of surgical ICU patients in Detroit, 50% of which received vitamin D supplements | n = 66 | Seventy-four percent < 20 ng/mL, which was associated with non-significant trends in increased infection and sepsis |
| 2011 | Vankatram et al. ⁴⁷ | Retrospective cohort of patients in a New York medical ICU with 25D drawn within 24 h of admission | n = 437 | 25D < 20 ng/mL was associated with hospital mortality |
| 2011 | Braun et al. ⁴⁹ | Retrospective cohort of patents admitted to 2 Boston ICUs who had a 25D level 7–365 d before admission | n = 2,399 | 25D < 15 ng/mL associated with increased mortality and blood culture positivity. Mortality association not modified by presence of sepsis |
| 2011 | Ginde et al. ⁵² | Prospective cohort pilot of adults admitted from Emergency Department with suspected infection | n = 81 | Seventy-nine percent with 25D < 30 ng/mL and associated with increased severity sepsis at admission and 24 h |
| 2012 | Braun et al. ⁵⁰ | Retrospective cohort of patents admitted to 2 Boston ICUs who had a 25D level 7 d before or after ICU admission | n = 1,325 | 25D < 15 ng/ml associated with increased mortality which was not modified by the presence of sepsis |

25D, 25-hydroxyvitamin D.

patients admitted to medical and surgical ICUs with a 25(OH)D drawn within the year prior to admission. The data showed a 1.3- and 1.7-fold increase in all-cause mortality among vitamin D insufficient and deficient groups (< 30 ng/mL and < 15 ng/mL) respectively and a significant increase in blood culture positivity.⁴⁹ The other analysis was of 1,325 patients with a 25(OH)D drawn 7 d before or after ICU admission and revealed a significant association between vitamin D deficiency (< 15ng/mL) and increased mortality at 30, 90 and 365 d.⁵⁰ The vitamin D-mortality association in both analyses was not modified by the presence of sepsis.^{49,50} Highlighting the complexity of confounding in critically ill and septic patients, a prospective study by Cecchi et al. found a relationship between mortality and vitamin D deficiency among 170 patients with severe sepsis and septic shock that became insignificant after adjustment.⁵¹

A pilot study by Ginde et al. more specifically looked at low vitamin D and its effects on the severity of sepsis. The investigators followed 81 patients suspected of having an infection in the Emergency Department and examined their severity of illness in comparison to vitamin D status. They found that patients with serum 25(OH)D concentrations less than 30 ng/mL were more likely at enrollment to have severe sepsis and SOFA (Sepsis-related Organ Failure Assessment) scores ≥ 2 and more likely at 24 h to have severe sepsis, SOFA scores ≥ 2 , APACHE II (Acute Physiology and Chronic Health Evaluation II) scores ≥ 25 and dysfunction of two or more organ systems.⁵²

Overall, the evidence suggests associations between vitamin D depletion and critical illness-related outcomes with the link to

sepsis less clear. These relationships are likely confounded by many common risk factors such as age, socio-economic status, obesity, and chronic illness. In regards to the last risk factor, chronically ill and debilitated individuals likely spend more time indoors with consequent less sun exposure and more vitamin D deficiency. These confounding associations make it difficult to prove causality in critical-illness outcomes. In addition to these epidemiological phenomena, sepsis therapy may also confound this relationship. One study demonstrated this by showing that the hemodilutional effects of fluid resuscitation can decrease serum 25(OH)D concentration by 35%.⁵³ These issues reveal the complexity of research in this field and the important confounders that must be accounted for in future studies.

Vitamin D and the Seasonal and Racial Variation in Sepsis

While no studies have directly examined the association between the seasonal and geographic variations of serum 25(OH)D concentrations and the incidence of sepsis, evidence suggests possible parallels.⁵⁴ A study surveying the national hospital discharge database from 1979 to 2003 in the USA, showed a significant seasonal variation of sepsis and severe sepsis with the highest incidences in the winter and the lowest in the fall, with a parallel variation in the incidence of the most common cause of sepsis, respiratory infections.⁵⁵ Furthermore, the Northeast USA showed the greatest seasonal variation in sepsis incidence compared with the Southern USA which showed the least variation.⁵⁵

These patterns parallel the annual variations in serum 25(OH)D concentrations, with peak concentrations in the fall and a nadir after the winter.⁵⁶ This is in part explained by the elliptical orbit of the earth around the sun, changing the solar zenith angle throughout the seasons, which effects the amount of ultraviolet-B (UVB) radiation reaching the Earth's surface.⁵⁷ Interestingly, this seasonal variation of vitamin D synthesizing radiation is less pronounced nearer the equator where the seasonal variation of sepsis and respiratory infections may be lower.^{57,58} This speculation, however, oversimplifies the other geophysical factors that affect vitamin D synthesis, including cloud and ozone cover, altitude and surface reflectivity.⁵⁷

There are also human factors that effect vitamin D synthesis including sun protective behaviors and skin pigmentation, the latter of which may also point toward links between vitamin D and racial differences in sepsis. Studies have shown that in the US, blacks are nearly twice as likely to develop sepsis as whites,³⁹ develop more infections⁵⁹ and have higher rates of organ dysfunction with sepsis.⁶⁰ While vitamin D status was not included in these studies, blacks tend to have lower serum 25(OH)D concentrations than whites. In a recent review, Grant outlined cross-sectional data showing serum 25(OH)D concentrations to be 16 ng/mL, 21 ng/mL and 26 ng/mL among blacks, Hispanics and whites in the US.⁶¹ This could be explained by the fact that increased skin pigmentation leads to less production of vitamin D as melanin absorbs and competes for UVB

radiation.⁶² With vitamin D's pleiotropic effects on bodily health, it has been suggested that it may be a contributing cause for racial disparities across many diseases⁶¹ and its effects on the immune system may provide a connection with the higher rates of infection and sepsis in blacks. As with the seasonal variation hypothesis, there are no studies that directly examine this relationship, but the speculations warrant further investigation.

Conclusion

The multiple functions of vitamin D in the immune system's response to infection suggest it may be an integral component in combating sepsis (Fig. 1). The basic science data point toward vitamin D's role in the optimal functioning of the innate immune system, in part by producing AMPs such as LL-37; while seeming to temper the inflammatory cascade induced by LPS. The early clinical data on its role in preventing and attenuating infections has suggested a link but intervention trials have produced mixed results, requiring larger randomized controlled trials to help define the relationship. Furthermore, clinical data also point toward a role of vitamin D and critical illness but a direct relationship with sepsis and its severity and outcomes is yet to be determined by further research. Some interesting parallel patterns between vitamin D and seasonal and racial variations in sepsis are currently speculative but interesting questions to be explored. In conclusion, the current

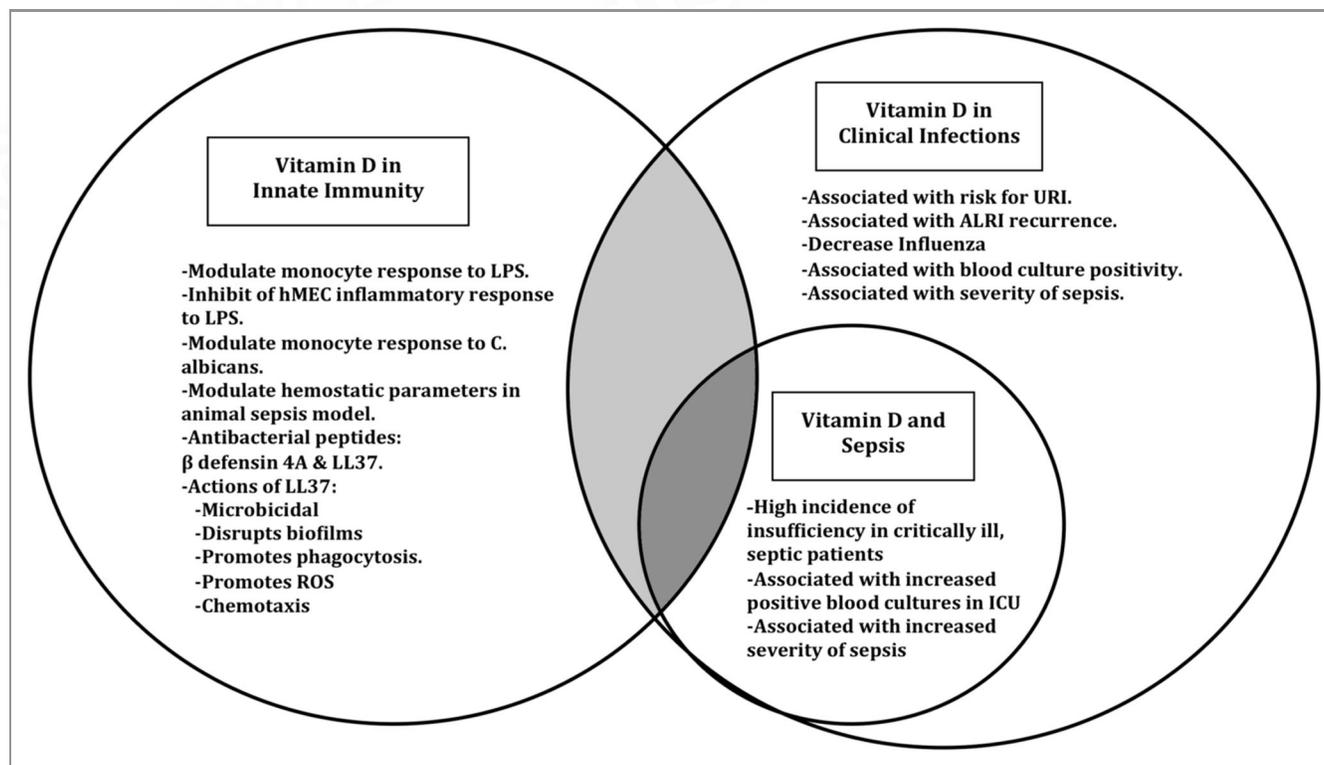


Figure 1. Morbidity and mortality vitamin D insufficiency and sepsis. Venn diagram reflecting the links between vitamin D's roles in innate immune function, clinical infections and sepsis in the critically ill. The intersections represent the potential increased morbidity and mortality resulting from vitamin D insufficient states predisposing to and exacerbating sepsis.

picture of vitamin D and sepsis is one of a research field early in its course with many important links that provide fertile ground for further investigation. Such investigation is warranted as vitamin D is inexpensive and safe to administer and even incremental benefits in the outcomes of sepsis may be enacted on a scale to produce a significant public health impact (Fig. 1 and Tables 1–3).

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