

An update on the association of vitamin D deficiency with common infectious diseases

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Abstract: Vitamin D plays an important role in modulating the immune response to infections. Deficiency of vitamin D is a common condition affecting both the general population and patients in health care facilities. Over the last decade, an increasing body of evidence has shown an association between vitamin D deficiency and an increased risk for acquiring several infectious diseases, as well as poorer outcomes in vitamin D deficient patients with infections. This review details recent developments in understanding the role of vitamin D in immunity, the antibacterial actions of vitamin D, the association between vitamin D deficiency and common infections (like sepsis, pneumonia, influenza, methicillin-resistant *Staphylococcus aureus*, human immunodeficiency virus type-1 (HIV), and hepatitis C virus (HCV)), potential therapeutic implications for vitamin D replacement, and future research directions.

Key words: vitamin D, immunity, pneumonia, HIV, sepsis, MRSA, therapy

Introduction

Recently our understanding of the role that vitamin D plays in human health and disease has undergone a major renaissance. Long recognized for its function in regulating calcium-phosphate homeostasis, vitamin D is now seen as an important modulator of the immune response to infection (Hewison 2012). Just as significantly, vitamin D deficiency is being increasingly associated with a wide range of medical conditions including infectious diseases. The circulating form of vitamin D, 25-hydroxy vitamin D [25(OH)D] is measured in serum and is considered the most accurate marker of vitamin D status (Hewison 2012). Vitamin D deficiency is defined as a 25(OH) vitamin D level of ≤ 20 ng/mL and insufficiency as a level between 21 and 29 ng/mL (Holick 2007). Severe deficiency [$25(\text{OH})\text{D} < 8$ ng/mL] has been shown to significantly increase the likelihood of developing infections such as bacteremias among medical inpatients, even after adjusting for age (Marra et al. 2014). Vitamin D is known to exert a range of effects on both the innate and adaptive immune systems. For example, it is necessary for effective macrophage responses to HIV and *Mycobacterium tuberculosis* (MTb), with low levels associated with more rapid disease progression (Campbell and Spector 2012). Vitamin D also stimulates the production of cathelicidin, which is a peptide found in the lysosomes of macrophages and polymorphonuclear leukocytes (Hewison 2012).

The purposes of this article are to discuss recent data on the role of vitamin D in innate and adaptive immunity, along with the association between vitamin D deficiency and certain infectious diseases including sepsis, respiratory infections like influenza and MTb, methicillin-resistant *Staphylococcus aureus* (MRSA), human immunodeficiency virus type-1 (HIV) and hepatitis C virus (HCV). Adjunctive therapy with vitamin D

replacement on infectious risks and severity of infection and directions for future research will be presented.

Vitamin D and the Immune System

Innate immunity

Important components of the innate immune response, toll-like receptors (TLRs) elicit direct antimicrobial activity against intracellular bacteria such as MTb. Macrophages are activated by TLRs through up-regulated expression of the vitamin D receptor (VDR) and the vitamin D-1-hydroxylase genes leading to the induction of the antimicrobial peptide cathelicidin, which kills intracellular MTb (Liu et al. 2006). Data from this seminal study also showed that individuals with low 25(OH)D were inefficient in supporting cathelicidin messenger RNA induction. A similar genome-wide analysis of dendritic cells (DCs) revealed diverse responses to vitamin D including a strong impact on metabolic pathways involving lipids, glucose, and oxidative phosphorylation that may affect the production of or the response to reactive oxygen species generation (Ferreira et al. 2012). Moreover, 1,25-dihydroxy vitamin D3 (1,25 D) boosts infection-stimulated cytokine/chemokine responses including interleukin 1 β (IL-1 β) expression by a direct transcriptional mechanism (Verway et al. 2013). IL-1 β modulates epithelial production of the antimicrobial peptide DEFB4/HBD2, thus playing a role in paracrine signaling.

Once intracellular pathogens like MTb are internalized by a phagocyte, they are next encapsulated into phagosomes. These phagosomes are joined to lysosomes forming phagolysosomes within which bacterial killing occurs (Vergne et al 2004). MTb have developed mechanisms to subvert the formation of phagolysosomes (Vergne et al. 2004). One way the host cell can restore pathogen encapsulation is autophagy, a process

whereby a double-membrane autophagosome surrounds the organism before fusion with the lysosome occurs, followed by degradation and recycling of nutrients (Levine et al. 2011). Vitamin D is a known inducer of autophagy (Wang et al. 2008) and more recently it was discovered that monocyte autophagy following activation of TLR2/1 involves enhanced expression of VDR and cathelicidin induction (Shin et al. 2010). Furthermore, using an experimental model of human endothelial cells subjected to oxidative stress, investigators found that pretreating the cells with either vitamin D alone or in combination with a specific vitamin D ligand (ZK191784) prevented cell death by modulation between autophagy and apoptosis (Uberti et al. 2014). This effect likely occurs through the inhibition of superoxide anion generation which maintains mitochondria function and cell viability, activation of survival kinases and nitric oxide production. Indeed, nitric oxide is produced in murine macrophages as part of the innate immune response to MTb with bactericidal results, although it is unclear if a similar pathway exists in human macrophages (Kohchi et al. 2009). In summary, experimental evidence shows vitamin D plays an important role in the innate immune response including the induction of cathelicidin, stimulation of cytokines and induction of autophagy.

Adaptive Immunity

Vitamin D has been shown to exert a number of modulating effects on T cells (Figure 1). For example, 1,25D induces the differentiation of native T cells to regulatory T cells (Treg) through paracrine effects on CYP27B1/VDR-expressing DCs (Jeffery et al. 2012). The rate limiting enzyme for metabolism of vitamin D is 1 α -hydroxylase. Recently it was shown that CD8+ T cells in mice express 1 α -hydroxylase (Ooi et al.

2014). Whether human CD8+ T cells also express 1 α -hydroxylase remains to be elucidated. The main effect of 1,25D on T cells appears to be the development and differentiation of T helper type 1 (Th1) and T helper type 2 (Th2) cells, with 1,25D favoring Th2 (Mora et al. 2008). The balance between Th1 and Th2 has important consequences to the immune response to infection. Th1 cells produce pro-inflammatory cytokines like interferon gamma (INF- γ), while Th2 cells produce anti-inflammatory ones like IL-4 and IL-5. In promoting Th2 development, vitamin D thereby limits tissue damage from the inflammatory response (Hewison 2012).

While most reports of the effects of vitamin D on adaptive immunity have focused on T cells, experimental data from over 25 years ago showed 1,25D could suppress the development of immunoglobulin-secreting B cells after mitogenic stimulation (Iho et al. 1986). Moreover, 1,25D can also suppress the differentiation of two types of B cells, plasma cells and class-switched memory cells (Chen et al. 2007). Data from another study show that 1,25D enhances IL-10 expression of activated B cells more than threefold by recruiting the vitamin D receptor to the promoter of IL-10 and by modulating calcium-dependent signaling (Heine et al. 2008).

Role of Vitamin D Deficiency in Specific Infections

Sepsis

A major cause of significant morbidity, sepsis has a short-term mortality of approximately 20% among patients presenting to emergency departments in the U.S. (Wang et al. 2007). Vitamin D deficiency is highly prevalent in different patient populations with sepsis including the elderly and African Americans (Watkins et al. 2011). Furthermore, septic patients admitted to intensive care units (ICUs) with low

25(OH)D have lower mean levels of cathelicidin and vitamin D binding protein which likely leads to reduced monocyte autophagy (Jeng et al. 2009). There have been several observational studies that showed an increased mortality in septic patients with vitamin D deficiency. One large multicenter study reported a significantly higher rate of positive blood cultures (odds ratio [OR] 1.64; 95% confidence interval [CI]: 1.05 to 2.55; P = 0.03) in patients with a 25(OH)D level <15 ng/ mL, and this level was also a significant predictor of short- and long-term all-cause mortality (Braun et al. 2011). This same research group recently reported a two-center observational study of 3,386 septic patients that showed 90 day mortality was 1.6 times greater in patients with preadmission 25(OH)D levels less than 30 ng/mL (Moromizato et al. 2014). Notably, these investigators defined a preadmission level as one obtained between 1998 and 2011, a rather long timeframe. In another observational study, patients with sepsis and 1,25D \leq 13.6 pg/mL had a 30 day survival of 57.1% compared to 91.7% in patients with a level $>$ 13.6 pg/mL (Nguyen et al. 2013). Thus, it seems logical to hypothesize that active replacement of vitamin D in deficient patients with sepsis would be beneficial. Indeed, the recommendation for an adequately powered, randomized, prospective, placebo-controlled clinical trial to investigate the issue has been advocated (Watkins 2012).

The rate of sepsis is known to fluctuate based on seasonality with a higher prevalence in the winter months (Danai et al. 2007). In 655 patients with sepsis admitted to an ICU in Austria, the highest mean 25(OH)D value was observed in August (28.0 ± 13.9 ng/mL) which was significantly higher than the mean in the months of March (15.4 ± 8.4 ng/mL, $P < 0.001$), October (15.3 ± 4.9 ng/mL, $P < 0.001$) and November (14.8 ± 9.0

mg/mL, P <0.001) (Amrein et al. 2014). However, some pathogens are also seasonal which makes interpretation of this kind of data complicated.

Respiratory infections

Mycobacterium tuberculosis remains a major public health scourge, with increasing rates of multi-drug resistant strains being reported worldwide (Gunther 2014). New York City, which had a peak of MTb cases in 1992 followed by a steady decline, saw a 1% increase in 2013 (Macaraig et al. 2014). Vitamin D deficiency is common in patients with active MTb (Kim et al. 2013). In the pre-antibiotic era, cod liver oil, which is high in vitamin D, was used to treat MTb and other pulmonary infections (Watkins et al. 2011). The mechanism underlying this process is likely the inhibition of MTb growth in macrophages through the induction of autophagy by 1,25D, as well as an autophagic flux from cathelicidin (Campbell and Spector 2012). Intracellular MTb induces the accumulation of lipid droplets within macrophages, which the organism needs for growth. Using transcriptome analysis, researchers recently demonstrated that treating MTb-infected macrophages with vitamin D ended the intracellular lipid droplet accumulation (Salamon et al. 2014). Clinical studies on vitamin D supplementation in deficient individuals with active MTb have been disappointing. In a randomized, double-blind, placebo-controlled trial involving patients with MTb in Guinea-Bissau, supplementation with vitamin D did not lead to an improvement in clinical severity or 12-month mortality (Wejse et al. 2009). However, the relevance of this negative result is questionable given that the intervention did not influence participants' vitamin D status. Furthermore, a slight beneficial effect was noted among patients with MTb and low vitamin D, but the study was not significantly powered to detect such a difference. Bolus

vitamin D dosing was utilized (100,000 IU initially and repeated at 5 months and 8 months after study inclusion) instead of daily dosing, which may have confounded the results as well. Another randomized, placebo-controlled trial showed that vitamin D supplementation did not significantly affect time to sputum culture conversion except in a subgroup of patients with a particular kind of vitamin D receptor polymorphism (Martineau et al. 2011). Further analysis by these same investigators found that vitamin D supplementation modulated biomarkers of inflammation and immune function in patients with MTb (Coussens et al. 2012). However, this latter study has been criticized for violating trial randomization and not following accepted approaches to subgroup analysis (Grey and Bolland 2012). While these trials may have had methodological problems, available data do not suggest that supplementing vitamin D in patients with MTb, even in those who are deficient, has a positive impact on the clinical course of the disease. Furthermore, a recent meta-analysis that included five randomized controlled trials with 841 patients found no beneficial effects for vitamin D supplementation in the treatment of MTb (Xia et al. 2014).

The role of vitamin D deficiency in patients with pneumonia has also been investigated. Using dendritic cells stimulated with pneumococcal peptidoglycan, investigators found that vitamin D enhances innate immunity including TLR2, IL-1 β , and the β -defensin hBD-3 while depressing adaptive immune responses (Olliver et al. 2013). Data from a U.S. national health survey showed participants with 25(OH)D levels <30 ng/mL had a 56% higher risk of acquiring community-acquired pneumonia (CAP) within 1 year compared to those with levels > 30 ng/mL (Quraishi et al. 2013). In a prospective cohort of 112 patients admitted during the winter to a hospital in New Zealand, those

with 25(OH)D deficiency (defined as <30 nmol/L) had an increased 30-day mortality compared to patients with 25(OH)D levels >30 nmol/L (OR: 13.5; 95% CI: 2.6-69.1; P = 0.002) (Leow et al. 2011). Another prospective cohort study on CAP showed a significant association between low 1,25D and a disease severity score (P = 0.011) but not between 25(OH)D and the severity score (P = 0.325) (Pletz et al. 2014). Also, low vitamin D levels were associated with longer hospitalization (P < 0.001) but not fatal outcome (P = 0.626). A 25(OH)D level <37 nmol/L measured up to 15 months prior to hospitalization was associated with an increased odds of CAP (OR: 2.57; 95% CI: 1.08-6.08; P = 0.03) in a recent retrospective cohort study (Jovanovich et al. 2014). These data were substantiated by a meta-analysis of 5,660 patients from 11 placebo-controlled studies that found a protective effect from vitamin D against respiratory tract infections (OR: 0.64; 95% CI: 0.49-0.84) (Bergman et al. 2013). Notably, the protective effect was larger with once-daily dosing compared to bolus dosing. However, the authors suggested the results may have been influenced by publication bias and the true relationship between vitamin D and respiratory tract infections needs further clarification. The pathogenesis of CAP remains poorly understood and determining the risk factors that lead to its development is an important area for further investigation.

The efficacy and emerging resistance of antiviral agents against influenza virus, especially the neuraminidase inhibitors, is limited (Jefferson et al. 2014). Thus, novel approaches for treating influenza are needed such as stimulating the host immune response. While not fully elucidated, the antiviral activity of vitamin D likely results from modulation of cathelicidin and human beta defensin 2, as well as the release of reactive oxygen species (Beard et al. 2011). A randomized, controlled trial from New York found

no difference in the incidence or severity of upper respiratory infections during the influenza season between one group of adults who received 2,000 IU of vitamin D3 daily for 3 months compared to another group who received placebo (Li-Ng et al. 2009). However, both groups had high baseline levels of 25(OH)D and patients self-reported their illnesses by questionnaires, which may have led to reporting bias. Another study found vitamin D deficiency was not associated with higher antibody responses to influenza vaccination in adults over age 50, but interestingly led to a greater frequency of post-vaccination seroprotection for seasonal H1N1 (Sundaram et al. 2013). Finally, vitamin D supplementation was not effective in reducing the risk of influenza-like illness during the H1N1 epidemic of 2009 among adults, although the investigators did not measure vitamin D levels pre- or post-supplementation (Jorde et al. 2012). Vitamin D supplementation in influenza has not shown much benefit so far, although more robust prospective randomized clinical trials are warranted.

MRSA

Studies on vitamin D deficiency and the association with MRSA infections are limited. In an adjusted logistic regression analysis, individuals with vitamin D deficiency were shown to have a significantly increased risk of MRSA carriage (OR: 2.04; 95% CI: 1.09-3.84) (Matheson et al. 2010). Another report showed patients with MRSA infections and vitamin D deficiency had higher health care-associated costs and resource utilization compared to patients with normal vitamin D levels (Youssef et al. 2012). Whether vitamin D supplementation in deficient patients with MRSA infections will improve outcomes remains to be determined.

HIV

There have been several reviews recently published on vitamin D deficiency in HIV-infected individuals and is an area of active research (Lake et al. 2011), (Griffin et al. 2012), (Pinzone et al. 2013). Vitamin D deficiency is common in HIV patients. In a cross-sectional study involving a cohort of 263 outpatients with HIV, 36% were found to have severe vitamin D deficiency (Ansemant et al. 2013). A 25(OH)D level < 30 ng/mL has been associated with diminished late CD4 cell recovery after antiretroviral therapy (ART) initiation (Aziz et al. 2013). This is most likely due to late vitamin D-associated production from naive CD4 T-cells during immune reconstitution. Low 25(OH)D is also associated with progression to AIDS and is a prognostic factor for short term mortality in HIV patients (Shepard et al. 2014). Moreover, baseline 25(OH)D levels <32 ng/mL correlate with HIV disease progression and death along with virologic failure after the initiation of ART (Havers et al. 2014). Low 25(OH)D does not appear to predispose to or affect the clinical course of cryptococcal meningitis in HIV-infected patients (Jarvis et al. 2014).

Efavirenz, a non-nucleoside reverse transcriptase inhibitor, is one of the most commonly used drugs in combination therapy to treat HIV infection. In a randomized, double-blind, phase 3 trial, HIV patients who received efavirenz had significantly lower 25(OH)D levels at 48 weeks compared to those who received rilpivirine (-2.5 ng/mL; $P < 0.0001$ vs. no change) (Wohl et al. 2014). In contrast, boosted protease inhibitor monotherapy appears to causes less risk for developing vitamin D insufficiency or deficiency (Cervero et al. 2013). HIV-infected individuals not on ART were recently shown to have cathelicidin levels significantly lower than HIV-negative controls ($P = 0.045$) and HIV-positive patients on ART ($P = 0.045$) (Honda et al. 2014). Thus,

untreated HIV may contribute to lower cathelicidin levels and ART may potentially reduce this effect.

HCV

Vitamin D levels may affect the severity of HCV-associated liver disease. However, data conflict on the role vitamin D plays in disease progression. Some studies done with HCV-mono-infected populations demonstrate that lower 25(OH)D levels result in a reduced likelihood of achieving a sustained virologic response with antiviral treatment (Falletti et al. 2012), (Lange et al. 2011), while another found no clear association (Kitson et al. 2012). It is plausible that differences within the patient populations in each study (e.g. ethnicity) could explain the discordant results. Among a group of HCV-infected male veterans, African Americans with 25(OH)D levels > 50ng/mL had a significantly elevated risk of advanced fibrosis ($P = 0.03$) while those who were 25(OH)D insufficient or deficient had a two-fold higher hepatic inflammatory activity risk ($P = 0.06$) (White et al. 2013). No risk was found among whites for advanced fibrosis or hepatic inflammation based on vitamin D levels. A recent meta-analysis that included 11 studies with 1,575 total HCV-infected subjects found high rates of SVR in subjects with 25(OH)D levels >30 ng/mL as well as those who received vitamin D supplementation (Villar et al. 2013). The studies included in this meta-analysis were conducted before the widespread use of the direct acting antiviral agents like sofosbuvir and whether vitamin D levels affect the response to these novel agents is a topic for further investigation. Among HIV/HCV coinfected patients, adjusted logistic regression analyses showed that 25(OH)D deficiency was associated with severity of liver disease (OR: 8.47; 95% CI: 1.88-38.3; $P = 0.005$) but not sustained virological response (SVR)

(Guzmán-Fulgencio et al. 2014). Another study on HIV/HCV co-infected patients found an association between 25(OH)D levels <20 ng/mL and higher rate of liver fibrosis progression (OR: 5.62; 95% CI: 2.05-15.38; P = 0.001) (Mandorfer et al. 2014).

Therapeutic Role for Vitamin D and Future Research Directions

The role of vitamin D in infectious diseases is not fully understood, although some emerging data suggest it exerts a protective effect in certain situations. Vitamin D up-regulates multiple genes that modulate β -defensin 2 and cathelicidin production and autophagy by macrophages - key defenses against intracellular pathogens. Despite theoretical benefit, clinical studies of vitamin D supplementation have produced mixed results although this might be due to methodological differences, confounding factors and dosing strategies between the studies. For example, various populations, ethnic groups, baseline 25(OH)D levels, and dosing regimens of vitamin D supplementation have been studied. It is also important to note that genetic polymorphisms of the VDR lead to different susceptibilities to certain infections (e.g. tuberculosis and HIV) and treatment responses (Rathored et al. 2012), (Torres et al. 2010). Further studies on VDR polymorphisms and their role in the progression of infections are warranted. Areas of uncertainty remain regarding the role of vitamin D in adaptive immunity, such as T-cell activation. Moreover, the mechanism for the association between vitamin D and HCV-induced liver fibrosis needs to be clarified.

Outside of the laboratory, clinical questions remain such as whether 25(OH)D repletion in deficient patients will decrease risk for and lead to better outcomes in community-acquired pneumonia, MRSA infections and sepsis, to name a few. Indeed, a major report from the Institute of Medicine recommended that more randomized

controlled trials be conducted to assess the impact of 25(OH)D on extra-skeletal health (Ross et al. 2011). Clinical trials will be challenging because of uncertainty regarding optimal vitamin D dosing and the interaction of vitamin D with genetic polymorphisms specific for certain populations. Investigators need to carefully consider what outcomes to measure in these trials for them to be useful at the bedside. Another important question that is not yet answered is whether vitamin D can be used as therapy in infections or is it better for preventing them? (Hewison 2012). Finally, whether the association between infections and vitamin D deficiency is causal or instead due to impaired extra-renal activation and function of vitamin D remains to be determined.

Conclusions

While the association between vitamin D and the immune system has been known for decades, only recently has a more nuanced understanding of its role in the elimination of pathogens like *M. tuberculosis* developed. Vitamin D deficiency is a common condition affecting diverse patient populations and appropriate vitamin D supplementation is generally safe and inexpensive. Given current concerns about increasing rates of antibiotic-resistant pathogens like MRSA, vitamin D might become a useful adjunctive therapy for a wide range of infectious diseases. Hopefully, robust clinical trial data will emerge to help clarify and guide therapeutic decisions.

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