

Vitamin D for Treatment and Prevention of Infectious Diseases: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Objective Vitamin D is the precursor to a steroid hormone primarily known for its role in regulating calcium homeostasis and skeletal health. Vitamin D also has non-skeletal functions that may play a role in susceptibility to various infectious and autoimmune conditions. Despite recent advances in understanding of the non-classical functions of vitamin D, little information is available regarding their clinical relevance for patient care. We review the existing human controlled intervention studies of vitamin D as adjunctive therapy in settings of infection, and provide recommendations for design and implementation of future studies in this field based on the evidence reviewed.

Methods We conducted a systematic review of randomized controlled clinical trials that studied vitamin D therapy for treatment or prevention of infectious diseases in humans. Studies from 1948-2009 were identified through search terms in PubMed and Ovid.

Results Thirteen controlled trials were identified by our search criteria. Ten trials were placebo controlled, and nine of the ten were conducted in a rigorous double-blind design. The selected clinical trials demonstrated significant heterogeneity in terms of baseline patient demographics, sample size, and vitamin D intervention strategies. Serious adverse events attributable to vitamin D supplementation were rare across all studies. Based on studies reviewed to date, the strongest evidence supports further research into adjunctive vitamin D therapy for tuberculosis, influenza, and viral upper respiratory illnesses. Aspects of study design are highlighted for the selected studies to help guide future clinical research in the field.

Conclusions More rigorously designed clinical trials are needed to further evaluate the relationship between vitamin D status and the immune response to infection, and to delineate necessary changes in clinical practice and medical care of patients with vitamin D deficiency in infectious disease settings.

INTRODUCTION

The link between vitamin D deficiency and susceptibility to infection has been suggested for longer than a century, with the early observation that children with nutritional rickets were more likely to experience infections of the respiratory system, leading to the coining of the phrase “rachitic lung”(1). The isolation of vitamin D₃ from cod liver oil, which was used to treat tuberculosis (TB) in the 1930’s, lead to its widespread use in TB treatment and prevention, until the introduction of anti-infective chemotherapy in the 1950’s (2). More recently, epidemiologic studies have demonstrated strong associations between seasonal variation in vitamin D levels and incidence of various infectious diseases, including septic shock (3), respiratory infection (4), and influenza (4,5).

Our understanding of vitamin D metabolism and its extra-skeletal functions has improved significantly over the past three decades. The discovery that vitamin D receptor (VDR) and 1 α -hydroxylase, the enzyme necessary for conversion of vitamin D into its active form, are present in cells of the immune system, including circulating mononuclear cells (6,7), has revolutionized the field of vitamin D immunology. Discovery of non-skeletal functions of vitamin D has re-invigorated interest in vitamin D as a potential modulator in a variety of disease states (8-10). Recent studies have demonstrated that vitamin D regulates expression of specific endogenous anti-microbial peptides in immune cells (11), leading to a potential role for vitamin D in modulating the immune response to various infectious diseases.

These findings highlight the need to refine our understating of the non-skeletal functions of vitamin D through future controlled studies of vitamin D supplementation and clinical outcomes in specific disease states. We focus on reviewing the existing human controlled intervention studies of vitamin D as adjunctive therapy in settings of infection, and provide recommendations for design and implementation of future studies in this field.

BACKGROUND

VITAMIN D AND BACTERIAL INFECTIONS

The pioneering work of Rook and Crowle in the 1980s demonstrated that vitamin D enhanced bactericidal activity of human macrophages against *Mycobacterium tuberculosis* (*M. tb*), the causative agent of TB (12, 13). This discovery led to a new era of interest regarding the role of vitamin D in determining pathogenesis and the immune response to bacterial pathogens. Liu and colleagues provided a key mechanism to how vitamin D may enhance innate immunity. This group demonstrated that stimulation of macrophage-bound Toll Like Receptor (TLR) 2 / 1 complex by *M. tb*-derived antigens up-regulates the expression of both vitamin D receptor (VDR) and CYP27b1, an enzyme that converts 25(OH)D to its active 1,25(OH)₂D form (11). Intracellular 1,25(OH)₂D generated through action of CYP27b1 then interacts with the VDR leading to induction of the antimicrobial peptide cathelicidin and killing of intracellular *M. tb* (11). In the state of vitamin D deficiency, the infected macrophage is unable to produce sufficient 1,25(OH)₂D to up-regulate production of cathelicidin.

While this anti-microbial mechanism of vitamin D has only been demonstrated in macrophages infected with *M.tb*, it is also well known that cathelicidin has broad-spectrum activity against a wide variety of other pathogens, including gram-negative and gram-positive bacteria, viruses and fungi (14). Vitamin D is also known to regulate the expression of β -defensin (15), another antimicrobial peptide with multiple effector functions within the immune system. Human endoscopy studies demonstrate that β -defensin is secreted in the gastric mucosa following infection by *Helicobacter pylori* (16), and may therefore constitute a major aspect of immune defense against this bacterial pathogen at the mucosal surface. Additional studies also suggest that vitamin D may up-regulate the oxidative burst in activated macrophages (17), thus augmenting another multi-purpose mechanism of bacterial killing. Studies of VDR polymorphisms in humans support the hypothesis that variability in vitamin D status and host genes encoding vitamin D responsive elements affect the immune response to

bacterial pathogens other than *M.tb* (18,19). Therefore, much of what we learn from the interaction between host vitamin D status and TB infection can inform our understanding of the immunomodulatory properties of vitamin D in other bacterial diseases, although more research is needed to help generalize this information to other clinical settings.

VITAMIN D AND VIRAL INFECTIONS

The seasonality of viral respiratory infections such as those caused by influenza virus (“the flu”) and rhinovirus (“the common cold”) has been observed in both popular (20) and scientific literature (21), and is understood to be a significant contributor to seasonal variations in human mortality (21). Based on these observations, Cannell et al have argued that vitamin D status may contribute in determining population susceptibility to seasonal epidemic outbreaks, as well as the degree of associated morbidity and mortality (5), **thus likely augmenting the effects of increased indoor confinement and circulating reservoirs of respiratory viruses in wintertime**. It is well known that often the exuberance of host immune response, rather than the viral pathogen itself, determines the clinical severity and mortality risk associated with viral diseases such as influenza (22, 23). Vitamin D modulates cytokine profiles in animal models of autoimmune disease through limiting excessive production of pro-inflammatory cytokines such as TNF α and IL-12, thus leading to suppression of inflammation (24). In addition, the antimicrobial peptides cathelicidin and β -defensin, regulated in part by vitamin D(11) (15), also play a major role in the immune defense of the respiratory system through direct inactivation of viral pathogens⁴⁰ and increased recruitment of phagocytic cells (25). Taken together, these studies support the hypothesis that optimal vitamin D status of the host may contribute key immunoregulatory functions in settings of viral respiratory infection by down-regulating overly exuberant (and thus toxic) cytokine responses, while allowing for improved clearance of various microbial species (5).

The relationship between vitamin D status and HIV infection is also capturing more attention in recent literature. It is uncertain at this point whether vitamin D status is associated with particular outcomes of HIV related disease, and potential for immunologic recovery with antiretroviral therapy. However, recent studies do suggest that there may be an increased prevalence of vitamin D deficiency in HIV infected patients compared to uninfected hosts, although these data remain conflicting (26, 27). Laboratory models of HIV infection demonstrated that pre-treatment of human monocytes and macrophages with 1,25(OH)₂D prevents HIV infection in certain cell-lines (28), while increasing HIV replication in others (29). Another recent study demonstrated that cathelicidin, the antimicrobial peptide regulated in part by vitamin D, may directly inhibit replication of HIV (30). Therefore, the relationship between vitamin D metabolism, HIV disease, and HIV therapy appears complex, and more studies are needed to help interpret the clinical significance of thus-far conflicting data on this topic.

VITAMIN D AND OTHER INFECTIONS

Information regarding potential immunomodulatory roles of vitamin D in settings of other infections, such as diseases caused by fungal, protozoal, or parasitic organisms is limited. There is a growing understanding, however, that vitamin D status of the host may impact the overall bias of the host immune response, where vitamin D repletion appears to favor a Th2 based cytokine profile which is responsible for the observed positive effects of vitamin D therapy in animal models of autoimmunity (24). This background of circulating cytokines is also important for maintaining effective protection and control of various extracellular pathogens, specifically parasitic, protozoal, and some fungal infections (31, 32). However, these findings appear counterintuitive to what is known about vitamin D – mediated effects on immune responses to intracellular pathogens such as *M. tb*, where effective Th1-driven granuloma formation favors containment of latent TB infection and prevention of progression to active TB disease (33). Therefore, more information is needed to help understand the balance between

cytokine responses, host vitamin D status, and subsequent host-pathogen interactions with regards to other classes of infectious agents.

METHODS

We conducted a systematic review of randomized controlled clinical trials that investigated the relationship between vitamin D therapy and clinical outcomes related to infectious diseases in humans. We reviewed the medical literature in PubMed and Ovid-Medline from 1948-2009 using combinations of search terms including “vitamin D2, ergocalciferol, vitamin D3, cholecalciferol, vitamin D analogue, vitamin D, rickets, infection, immunity, treatment, tuberculosis, upper respiratory infection, influenza, bacteria, virus, protozoa, helminth, fungi, trial, placebo, randomized.” No database restrictions were used. Resulting abstracts were screened, and cross-references were used to identify additional publications. Studies focusing on vitamin D supplementation as adjunctive therapy in cancer or autoimmune disease, studies conducted *in vitro* only or in animal models, studies with non-English manuscripts, studies lacking an adequate control arm, and studies of vitamin D given as part of combination micronutrient supplementation protocols were excluded.

RESULTS

We found 13 controlled trials that met our search criteria (34-46) (**Table 1**). Ten trials were placebo controlled (34-36, 39, 41-46), and nine of the ten were conducted in a double-blind design. Five of twelve trials(34-38) addressed vitamin D supplementation in subjects with bacterial infection, with four of the five trials evaluating vitamin D as adjunctive therapy in subjects with various forms of TB infection. Seven trials (39-44, 46) were predominantly focused on vitamin D in subjects with viral infections and one trial (45) was conducted in subjects with schistosomiasis, a helminth infection.

The selected clinical trials demonstrated significant heterogeneity in terms of baseline patient demographics, sample size, and vitamin D intervention strategies. Four of the thirteen trials were conducted in pediatric populations (37, 40, 44, 45), while three other trials were in either postmenopausal (41) or elderly patients (38, 42). Sample size ranged from 24 subjects in a pediatric TB trial (37) to 3,444 subjects participating in a study of vitamin D and infection in the elderly (42). Co-morbid conditions also varied among the study populations, with inclusion of some HIV-infected patients in a large TB treatment trial (34), and one study being conducted exclusively in patients receiving hemodialysis (39).

Seven of the thirteen trials specified whether ergocalciferol (vitamin D₂) or cholecalciferol (vitamin D₃) was used (34, 35, 38, 41, 42, 44, 46); with cholecalciferol being favored over ergocalciferol in all but one study (35). Vitamin D replacement strategies varied in terms of frequency and dose of therapy, ranging from 40 IU of vitamin D₃ given daily for 20 years to 100,000 IU bi-monthly for 12 months (**Tables 2-4**). Three studies utilized high-dose repletion regimens such as three doses of 100,000 IU given over 8 months (34), or 60,000 IU weekly for 6 weeks (40), or 600,000 IU given over 12 months(44). Two (34, 44) of the three trials favoring rapid high-dose repletion of vitamin D stores are also the most recently published studies in the group, both appearing in print in 2009. The total dose of vitamin D given to the intervention group of each of the studies differed significantly, and our analysis of study outcomes (**Table 1**) revealed no clear trend towards positive study results favoring either long term daily repletion versus bolus replacement.

Six of the thirteen clinical trials (34, 35, 37, 41, 44, 46), provided information regarding the effectiveness of their selected repletion strategy by reporting baseline and follow-up 25(OH)D or 1,25(OH)D levels in the intervention group as compared to control or placebo (**Tables 2-4**). Eleven of the thirteen studies enrolled patients irrespective of baseline vitamin D status. In contrast, one study only included patients with a baseline 1,25(OH)₂D level below normal range (39), and another study excluded patients with evidence of severe vitamin D

deficiency, defined by a baseline serum 25(OH) D level < 12ng/mL (44). It should be noted that serious adverse events, such as clinically relevant hypercalcemia as result of vitamin D supplementation, were rare across all studies. Two of the thirteen trials (39, 41) reported instances of hypercalcemia in a total of 3 subjects necessitating decrease or discontinuation of study medication.

VITAMIN D AND BACTERIAL INFECTIONS

Five human trials of vitamin D replacement as treatment or prevention of bacterial disease have attempted to translate the mechanism of vitamin D – mediated macrophage activation to the human host (**Table 2**). Four of the five studies were conducted in TB infected patients, and yielded mixed results. While the outcome of a translational study done by Martineau et al were encouraging, where administration of a single dose of 100,000 IU of ergocalciferol to PPD-positive contacts of active TB cases improved their immunologic control of BCG (an *M. tb* surrogate) in the peripheral blood (35), other trials focusing on clinical endpoints related to TB treatment have generated conflicting results (34, 36, 37). Two of the three clinical TB studies, Morcos et al and Nursyam et al (**Table 2**), demonstrated a positive outcome. Morcos et al (37) reported a benefit of increased weight gain and faster resolution of TB symptomatology in children treated with daily 1,000 IU of vitamin D as adjunct to standard TB therapy. Nursyam et al demonstrated significantly higher rates of sputum conversion to culture-negative in the group treated with 10,000 IU of vitamin D **daily** for 6 weeks compared to placebo (36). However, both studies failed to report baseline or follow-up serum 25(OH) D levels for either the intervention or control groups, leaving uncertainty as to the adequacy of repletion in each case. **Although Morcos et al did report 1,25(OH)₂D levels before and after vitamin D treatment (Table 2), these may not provide adequate reflection of overall vitamin D status of the study subjects (48).** In contrast, the most recent trial of vitamin D therapy in TB patients by Wejse et al did report a significant rise in serum 25(OH) D levels in the intervention group

receiving 100,000 IU vitamin D at baseline, 5 months, and 8 months of TB therapy (34). The authors report baseline levels of 25(OH)D increased from 31 ng/mL to 41 ng/mL and 39 ng/mL at 2 and 8 months of follow-up, respectively. However, perhaps surprisingly, the authors describe that similar 25(OH)D levels were reported at baseline, 2 months, and 8 months in the placebo group (34) (**Table 2**), which suggests that the vitamin D dose given to the intervention group was not sufficient to increase 25(OH)D levels beyond what would be observed with TB treatment alone, making interpretation of the data difficult. Additional variables, such as increased exogenous intake of vitamin D irrespective of group assignment, or an independent effect of improving nutritional status with TB therapy, may also be confounding the results of the study, which saw no difference in TB-related clinical outcomes between the two study groups (34). Recruitment and follow-up for the study took place over the course of 24 months, and it is unclear whether seasonal alteration in vitamin D status affected any study outcomes (34).

The last trial included in **Table 2** by Kawaura et al reported lower incidence of infection with *H. pylori*, the bacterial agent of peptic ulcer disease, in elderly women receiving vitamin D supplementation of 40 IU per day over several decades (38). Although the study is hypothesis-generating for future studies in this field, it is hampered by its primarily retrospective design, limited sample size (n=34), poor repletion potential of the very low vitamin D dose selected for the study, and failure to document baseline and follow-up vitamin D status in either the control or the intervention groups.

Therefore, the human data available to date regarding the potential value of vitamin D as adjunctive therapy in bacterial infection remains conflicting. Three of the four TB trials, and the one trial of vitamin D therapy to prevent *H. pylori*-related gastrointestinal disease, demonstrated positive outcomes, although these studies were hampered by significant limitations, such as poor sample size and limited information regarding the effectiveness of the repletion strategy. The most recent and the most rigorously designed trial of the series by Wejse et al demonstrated no clear benefit of adjunctive vitamin D therapy in TB treatment. As

discussed above, vitamin D given at doses higher than the total 300,000 IU given to the intervention group in this study, along with careful attention to potential confounders affecting vitamin D levels in the placebo group, may be necessary to improve the statistical power of future studies. More prospectively designed, intervention based trials are needed to further evaluate the relationship between adequate vitamin D repletion and treatment and/or prevention of bacterial infections such as TB, among others.

VITAMIN D AND VIRAL INFECTIONS

Although information from laboratory and animal models of viral infection in settings of vitamin D deficiency is becoming more available, few human trials have been done to help translate these data into potential clinical applications (**Table 3**). Our search identified seven controlled trials concerning outcomes related to human viral infections.

VITAMIN D AND UPPER RESPIRATORY VIRAL INFECTIONS

Four of the seven studies evaluated the frequency of respiratory infection or influenza in vitamin D treated subjects compared to control (40-42). An early trial by Rehman et al most closely resembles a case control study, where 27 children were selected based on clinical history of recurrent respiratory or antibiotic-requiring illness, and paired with age matched controls documented to be free of recurrent infection. Subsequent analysis revealed the recurrent illness group to have a much higher prevalence of sub-clinical rickets (i.e. pediatric vitamin D deficiency), and decreased recurrence of respiratory infection following a course of aggressive vitamin D repletion, given as 60,000 IU weekly for 6 weeks (40). However, despite its promising results, the study is subject to several pitfalls, including absence of placebo control arm, limited sample size, and limited documentation regarding effectiveness of the chosen vitamin D repletion regimen (**Table 2**), which may affect the generalizability and overall interpretation of the results.

The remaining three studies designed to evaluate the effect of vitamin D therapy in viral upper respiratory infection were performed in follow up to larger trials of vitamin D supplementation for bone loss and fracture prevention in older adults. The study by Avenell et al included a large sample size of 3,444 community-dwelling elderly adults who were given 800 IU vitamin D or placebo for longer than two years, as part of the Randomized Evaluation of Calcium or Vitamin D (RECORD) trial (49). This study failed to show a significant difference either in the primary endpoint of fracture prevention, or in the secondary endpoint of self-reported infection rate in the week prior to assessment, between the vitamin D and placebo groups (42) (**Table 3**). However, the results of RECORD study are complicated by poor observed compliance with supplements in the study population, with only 54.5% of subjects remaining compliant with study medication at 24 months of follow-up (42). Another trial by Aloia et al included 208 healthy post-menopausal African American women who were given 800 IU vitamin D daily or placebo for 2 years, followed by 2,000 IU daily for 12 months or placebo (41). Although the primary outcome of bone mineral density demonstrated no significant difference between the two groups (47), a lower rate of self-reported upper respiratory illness or influenza was observed in the intervention arm compared to placebo, and this effect was further magnified with an increase in the daily vitamin D dose from 800 IU daily to 2,000 IU daily (41). It should be noted that, in contrast to the study by Avenell et al which demonstrated relatively meager increases in serum 25(OH)D levels of the intervention group following vitamin D therapy (**Table 3**), the trial by Aloia et al reports follow up mean serum 25(OH)D levels commensurate with the current definition of vitamin D sufficiency at levels of 25(OH)D \geq 32 ng/mL (48). This difference in study design highlights the putative importance of ensuring adequate vitamin D repletion (at least >30-32 ng/mL) to maximize its extra-skeletal and immunomodulatory effects in future intervention trials.

However, a recently published dedicated follow up study by Li-Ng and Aloia et al, where 162 healthy adults were given 2,000 IU of cholecalciferol or placebo daily for 12 weeks during

the winter and spring months of 2007, showed no benefit in its two primary outcomes, incidence and severity of URI symptoms for the vitamin D group versus placebo (46). This lack of significant difference in outcome was observed despite appropriate increases in serum 25(OH)D levels in the intervention group, with a mean level of 25.72 ng/mL at baseline and 35.4 ng/mL at 12 weeks (**Table 3**). The authors emphasize that although no major benefit of URI prevention was observed in this study, the statistical trend did appear to favor the vitamin D group, which suggests that higher sample size and more robust vitamin D repletion, perhaps over a longer period of time, may be beneficial in design of future studies.

VITAMIN D AND VACCINATION

Two additional studies evaluated the role of vitamin D as adjuvant therapy to boost hepatitis B(39) and influenza vaccine responses (43) as a novel approach to using vitamin D as preventative therapy for viral infection. Moe et al treated 31 hemodialysis patients with the vitamin D analogue paricalcitol for 12 weeks (**Table 3**) to improve the blunted immunogenicity profile of hepatitis B vaccine seen in patients with end-stage renal disease and hemodialysis (50). Similarly, Kriesel et al administered single intramuscular doses of 40 IU of vitamin D or saline placebo to boost immune responses following influenza vaccination in 175 healthy volunteers (43). Neither study demonstrated a significant increase in hepatitis B or hemagglutination titers in the intervention group compared to placebo (**Table 3**). Future studies in the field of vitamin D and vaccine immunology should include a more rigorous focus on clinical and immunologic effectiveness of dose-finding repletion strategies and more detailed documentation of baseline and follow-up vitamin D levels after therapy.

VITAMIN D AND HIV

Although a small Norwegian study demonstrated an association between low 1,25(OH)₂D levels, rate of CD4 count decline, and HIV-related mortality (51), few prospectively

designed clinical studies have been done to determine any causal relationship between host vitamin D status, immunologic decline, and clinical outcomes in HIV-seropositive patients. Several large studies of multivitamin and micronutrient formulations containing modest doses of vitamin D have demonstrated some gains in morbidity and mortality when given to HIV positive patients in developing countries, especially those co-infected with *M.tb* (52, 53), but it is difficult to extrapolate any vitamin D-specific effects from these data.

Our search criteria identified one recent randomized placebo controlled trial of isolated vitamin D therapy in a pediatric HIV positive population. Arpadi et al reported administering 100,000 IU of cholecalciferol bimonthly or placebo over 12 months to 53 HIV positive children and adolescents with or without antiretroviral therapy to evaluate the effect of vitamin D treatment on immunologic and clinical outcomes such as weight gain, mean CD4 count, and adequacy of viral load control. Although 44.4 % of children in the vitamin D group were documented to have 25(OH)D levels of 30 ng/ mL or higher at the end of study follow up, the study did not demonstrate a statistically significant difference between the two groups in terms of gains in CD4 count or improvements in virologic control (44) . Given the potential antagonistic relationship between antiretroviral therapy and vitamin D metabolism, particularly its impact on 1,25 (OH)D, rather than 25(OH)D, levels, as suggested by the literature, future trials in this arena may benefit from study design that includes a larger study population, along with more aggressive vitamin D dosing to achieve levels of 25-OH D considered optimal, and stratification on the basis of the subjects' antiretroviral regimen. These steps may help to delineate nuances of the complex immunological phenomena associated with this disease process.

In summary, the role of vitamin D status in modulating host immune responses to viral infection, ranging from HIV to the common cold, appears complex, and few controlled clinical intervention studies have been carried out to help illustrate the full therapeutic potential of vitamin D as adjunctive or preventative strategy in these settings. Initial promising results from studies evaluating the prevalence of viral upper respiratory infection and influenza in vitamin D

treated subjects can inform future trials in this field. Additional information from both clinical and laboratory-driven studies is clearly needed to help elucidate the complex interplay between vitamin D status, vitamin D metabolism, and HIV infection in the human host.

OTHER INFECTIONS

Intervention trials of vitamin D in other infections, such as diseases caused by fungi, protozoa, or other parasites, are very limited. Our search identified only one such trial (**Table 4**) by Snyman et al where 59 adolescents received 40 IU of vitamin D or placebo daily for 5 days in a two-by-two factorial design with or without antiparasitic therapy for *Schistosoma haematobium* infection, a common parasitic illness in the developing world (45). The results of the study by Snyman et al contribute to the limited body of knowledge on this topic by demonstrating some positive effects on levels of activated eosinophils and *Schistosoma*-specific antibodies in the vitamin D group, although no overt clinical benefit was noted (45).

CONCLUSION

Recent studies have described an high prevalence of vitamin D insufficiency and overt vitamin D deficiency in human populations worldwide (48). As our knowledge of the extra-skeletal functions of vitamin D continues to grow, the clinical significance of maintaining vitamin D sufficiency becomes more apparent. Several of the studies reviewed here build on existing pre-clinical research in vitamin D immunology which demonstrates a likely connection between vitamin D depletion, susceptibility to infection, and clinical outcomes in a variety of infectious processes. Based on studies reviewed to date, the strongest evidence (in the form of rigorous clinical trials) supports further research into adjunctive vitamin D therapy for tuberculosis, influenza, and viral upper respiratory illnesses. Some of the studies discussed here also included non-specific outcomes demonstrating that adequate vitamin D status may decrease all-cause infection rates in the populations studied (39, 40, 42). Although these studies yielded mixed results (39, 42), future population based studies to evaluate broad effects of vitamin D supplementation on infection rates and total mortality may be warranted.

Taken together, results of the studies discussed here highlight the need for more research to further characterize the complex interplay between vitamin D deficiency and repletion and host response to infectious diseases, and to tease out specific, clinically relevant effects of vitamin D repletion in these settings. As result of this review, several themes emerge that should be considered in the design of future studies to evaluate the role of vitamin D therapy in treatment of infectious diseases. First, the therapeutic potential of vitamin D –based interventions can only be assessed if there is adequate documentation as to the effectiveness of the selected repletion regimen in terms of improving the host’s vitamin D status, i.e. raising serum 25(OH)D levels. Therefore, measurement and reporting of pre- and post- repletion serum 25(OH)D levels must be an essential component of future studies in this field. Second, recent strides towards defining “vitamin D sufficiency” as a serum 25(OH)D level > 30-32 ng/mL (48) create a good target to frame future studies of vitamin D supplementation, and to

standardize vitamin D repletion protocols. However, the immunomodulatory and antimicrobial effects of vitamin D may require higher serum levels, thus necessitating more aggressive dosing schemes, as suggested by the results of the TB treatment study conducted by Wejse et al in Guinea- Bissau (34) and the recent URI study conducted by Li-Ng and Aloia et al (46).

Therefore, dose-ranging studies may be necessary to establish repletion thresholds to guide further studies evaluating the extra-skeletal effects of vitamin D. Finally, other limitations similar to those identified in this review, such as limited sample size and poorly defined disease-specific treatment endpoints, may confound future prospective studies in the field of vitamin D immunology. Rigorous study design will be key in allowing clinical confirmation of hypotheses derived at the bench, in preclinical studies, or in animal models of vitamin D deficiency, and will help delineate necessary changes in clinical practice and medical care of patients with vitamin D deficiency.

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Table 1. Controlled Human Trials of Vitamin D Therapy for Infection Identified Through Systematic Literature Search

Study Pathogen ^{Ref}	Study Sample Size	Total vitamin D dose delivered / total dosing duration	Results summary
Bacterial			
<i>Mycobacterium tuberculosis</i> (34-37)			
Wejse et al (34)	n=365	300,000 IU / 8 mo	-- ^a
Martineau et al (35)	n=192	100,000 IU / one time	++ ^b
Nursyam et al (36)	n=67	420,000 / 6 wks	++ ^b
Morcos et al (37)	n=24	36,000 / 2 mo	+ ^c
<i>Helicobacter pylori</i> (38)			
Kawaura (38)	n=34	292,000 / 20 yrs	++ ^b
Viral			
Upper Respiratory Infection (URI) (40-42,46)			
Rehman et al (40)	n=27	360,000 IU / 6 wks	++ ^b
Aloia et al (41)	n=208	1,296,000 IU / 36 mo	++ ^b
Avenell et al (42)	n=3,444	576,000 IU / 24 mo	-- ^a
Li-Ng et al (46)	n=162	168,000 IU / 12 wks	-- ^a
Influenza (41)			
Aloia et al (41)	n=208	1,296,000 IU / 36 mo	++ ^b
Immune responses to vaccines against viruses (39, 43)			
Hepatitis B vaccine			
Moe et al (39)	n=31	144 ug paricalcitol / 12wks	-- ^a
Influenza vaccine			
Kriesel et al (43)	n=175	40 IU / one time	-- ^a
Human Immunodeficiency Virus (HIV) (44)			
Arpadi et al (44)	n=46	600,000 IU / 12 mo	-- ^a
Other			
<i>Shistosoma haematobium</i> (45)			
Snyman et al (45)	n=59	200 IU / 5 d	+ ^c
^a no study endpoints met, negative study			
^b all study endpoints met, positive study			
^c some study endpoints met, mixed results			

Table 2. Intervention Trials Evaluating Vitamin D Replacement as Treatment or Prevention in Bacterial Infection

Source Country Study type	Study Population n1=intervention (% HIV +) n2=placebo (% HIV +)	Main Endpoint(s)	Intervention	Mean baseline serum vitamin D level	Mean follow-up serum vitamin D level	Outcome
Wejse et al 2009 (34) Guinea- Bissau DB-PC-RCT	365 adults with pulmonary TB n1 = 187 (23) n2 = 178 (19)	Sputum conversion rates over time Points on TBscore clinical severity assessment tool 12 month mortality Lymphocyte subsets	100,000 IU D3 or placebo given at baseline, 5 mo and 8 months of TB therapy	n1 = 31 ng/mL ^a n2 = 32 ng/mL ^a	n1 = 41 ng/mL @ 2 months ^a , 39 ng/mL @ 8 months ^a n2 = 42 ng/mL @ 2 months ^a , 41 ng/mL @ 8 months ^a	No difference in sputum conversion, TBscore points, or mortality between groups No adverse events observed, 3 cases of mild subclinical hypercalcemia Increased CD4 counts and lower mortality in HIV-negative intervention subgroup, but difference failed to reach significance
Martineau et al 2007 (35) South Africa DB-PC-R-CT	192 adult TB contacts n1 = 64 (NR) n2 = 67 (NR)	Whole blood restriction of <i>BCG-lux</i> luminescence (a surrogate of <i>Mtb</i>) Whole blood interferon- γ release following stimulation by TB antigens	100,000 IU D2 or placebo given at baseline	n1= 14 ng/mL ^a n2 = NR	n1 = 27 ng/mL @ 6 weeks ^a n2 = NR	20.4% greater restriction of <i>BCG-lux</i> growth by blood from vitamin D group (p= 0.03) No observed difference in interferon- γ release between groups No adverse events observed
Nursyam et al 2006 (36) Indonesia DB-PC-R-CT	67 adults with smear positive pulmonary TB n1 = 34 (NR) n2 = 33 (NR)	Sputum smear conversion at 6 weeks Radiographic improvement	10,000 IU/day vitamin D or placebo given for first 6 weeks of TB treatment	NR	NR	23% greater sputum conversion rate at 6 weeks in vitamin D group compared to placebo (p = 0.002) 22.5% greater rate of radiographic improvement in vitamin D group compared to placebo (p = NR)
Morcos et al 1998 (37) Egypt R-CT	24 children (1.5-13yo) with pulmonary and extrapulmonary TB n1 = 12 (NR) n2 = 12 (NR)	Hypercalcemia Clinical improvement in TB related signs and symptoms Weight gain	1,000 IU/day D given in combination with standard TB therapy, or TB therapy alone	17.91 pg/ml for both groups ^b	n1 = 24.09 pg/ml ^b n2 = 20.83 pg/ml ^b	No observed difference in serum calcium levels between groups 16% higher rate of TB symptom resolution in vitamin D group (p = NR) Higher mean weight gain in vitamin D group (p < 0.005)
Kawaura et al 2006 (38) Japan CT	34 female nursing home residents (age 70-99) with or without osteopenia n1 = 15 (NR) n2 = 19 (NR)	Serum pepsinogen and gastrin levels Rate of <i>H. pylori</i> infection by serology	40 IU/day D3 given over twenty years for diagnosis of osteopenia or no supplement in non-osteopenic controls	NR	NR	Lower mean serum pepsinogen level in vitamin D arm (p < 0.05) Lower rates of positive <i>H. pylori</i> serology in vitamin D group (p<0.05)

DB=double blind; PC=placebo controlled; R = randomized; CT = clinical trial; NR = not reported; *H.pylori* = *Helicobacter pylori*; TB = tuberculosis

^aserum 25(OH)D

^bserum 1,25(OH)₂D

Table 3. Intervention Trials Evaluating Vitamin D as Treatment or Prevention of Viral Infection

Source Country Study type	Study Population n1=intervention (% HIV +) n2=placebo (% HIV +)	Main Endpoint(s)	Intervention	Mean baseline serum vitamin D level	Mean follow-up serum vitamin D level	Outcome
Moe et al 2001 (39) United States	31 hemodialysis patients with low PTH levels not otherwise on vitamin D therapy	DHT anergy to PPD, mumps, Candida, Trichophyton at baseline and 12 weeks	4 ug paricalcitol intravenously 3 times weekly during dialysis for 12 weeks or placebo	NR	NR	Higher rate of conversion from anergic to reactive skin test in paricalcitol group, although difference did not reach statistical significance (p = 0.09)
DB-PC-R-CT	n1 = 16 (NR) n2 = 15 (NR)	PBMC proliferative responses at baseline and 12 weeks PBMC cytokine production at baseline and 12 weeks Antibody titer in response to hepatitis B vaccine at 8 weeks Number of infections accessed by # of antibiotic prescriptions				No observed differences in PBMC proliferative or cytokine responses between groups No observed difference in antibody titers following vaccination with Hepatitis B vaccine No observed difference in infection rate between groups Paricalcitol group experienced more hypercalcemic events, although difference was not significant
Rehman et al 1994 (40) India	27 children (3-12 yrs old) with > 6 respiratory or antibiotic-requiring illnesses in preceding 6 months and 20 children (3-12 yrs old) with ≤ 1 respiratory or antibiotic-requiring illness in preceding 6 months , HIV status NR	Elevated serum alkaline phosphatase as proxy for diagnosis of subclincial rickets Frequency of respiratory infection in 6 months following intervention	60,000 IU D weekly x 6 weeks or no supplement in control group	NR	NR but study reports return of serum alkaline phosphatase to normal in majority of children in intervention group	Higher mean serum alkaline phosphatase in intervention group (p < 0.005) compared to control Difference in infection rates between groups no longer significant in 6 months following intervention (p = NR)
Aloia et al 2005 (47) United States	208 healthy postmenopausal women n1 = 104 (NR) n2 = 104 (NR)	Self-report of cold URI, or influenza as recorded every 6 mo while participating in study Seasonality of reported URI and	800 IU/day D3 for 24 months followed by 2,000 IU D3 daily for 12 months, or placebo for 36 months	n1 = 18.8 ng/mL ^a n2 = 17.2 ng/mL ^a	n1 = 28.4 ng/mL @ 3 months of 800 IU D3, 34.8 ng/mL @ 3 months of 2,000 IU D3 ^a n2 = NR	Lower rate of reported URI symptoms in intervention group compared to placebo (p<0.002) Placebo group more likely to experience symptoms in winter compared to intervention group (p = NR) Lower rate of reported URI symptoms while receiving 2,000 IU per day compared to 800 IU per day (p = NR)

influenza events

Avenell et al 2007 (42) England	3,444 elderly subjects participating in RECORD trial who also responded to a follow up questionnaire	Self-report of infection or antibiotic-requiring illness during the week preceding receipt of questionnaire in the mail	800 IU/day D3 for 24-62 months, or placebo	15.2 ng/mL in subsample of 60 patients selected across all groups	n2 = 24.9 ng/mL mean in subsample of 60 patients selected from vitamin D group	No difference in self-report of illness or antibiotic prescriptions between groups (p = 0.23 and 0.18, respectively)
DB-PC-R-CT	n1 = 1,740 (NR) n2 = 1,704 (NR)					
Li-Ng et al United States 2009 (46)	162 healthy adult outpatients n1= 84 (0) n2= 78 (0)	Self-report of URI symptoms Self-report of URI symptom severity	2,000 IU/day D3 for day for 12 weeks, or placebo	n1 = 25.72 ng/mL ^a n2 = 25.2 ng/mL ^a	n1 = 35.4 ng/mL ^a n2 = 24.4 ng/mL ^a	No difference in frequency (p = 0.56) or severity (p = 0.4) or duration (p = 0.86) of URIs incurred by both groups during study period, but statistical trend noted to favor vitamin D group in all outcomes
DB-PC-R-CT						
Kriesel et al 1999 (43) United States	175 healthy volunteers receiving killed influenza vaccination	Hemagglutination titers against H1N1, H3N2, and influenza B	40 IU vitamin D IM x 1 dose or saline placebo IM, administered with influenza vaccine	NR	NR	No difference in hemagglutination titers at 28 or 90 days post vaccination between groups
DB-PC-R-CT	n1 = 87 (NR) n2 = 88 (NR)					
Arpadi et al 2009 (44) United States	46 HIV-infected children and adolescents n1 = 29 (100%) n2 = 27 (100%)	Change in CD4 count and viral load during 12 mo study follow up	100,000 IU D3 bimonthly for 12 months, or placebo	n1 = 24.1 ng/mL ^a n2 = 23.6 ng/mL ^a	n1 = 32.4 ng/mL @ 12 months ^a n2 = 21.9 ng/mL @ 12 months ^a	No difference in change in CD4 count and viral load between groups at 12 months No episodes of hypercalcemia
DB-PC-R-CT						

Hypercalcemia

DB=double blind, PC=placebo controlled, R = randomized, CT = clinical trial, NR = not reported, PTH = parathyroid hormone, DHT = delayed hypersensitivity testing, PBMC = peripheral blood mononuclear cells, IM = intramuscularly, URI = upper respiratory infection

^aserum 25(OH)D

^bserum 1,25(OH)₂D

Table 4. Intervention Trials Evaluating Vitamin D as Treatment or Prevention of Parasitic Infection

Source Country Study type	Study Population n1=intervention (% HIV +) n2=placebo (% HIV +)	Main Endpoint(s)	Intervention	Mean baseline serum vitamin D level	Mean follow-up serum vitamin D level	Outcome
Snyman et al 1997 (45) South Africa	59 adolescents with <i>Schistosoma haematobium</i> infection	Cell subtype counts in peripheral blood	40 IU vitamin D daily x 5 days given alone, or in combination with praziquantel x 1 dose, or praziquantel alone x 1 dose, or placebo	NR	NR	Increased vacuolated eosinophils in D group compared to other three groups
PC-R-CT	n1 = 14 (D3) n2 = 16 (D3 + praziquantel) n3 = 14 (praziquantel) n4 = 15 (placebo), HIV status NR	Eosinophil cationic protein level in peripheral blood Specific IgE and IgG for whole- worm antigen in peripheral blood Egg shedding in the urine				Decreased eosinophil cationic protein in D group compared to other three groups Higher titers of <i>Schistosoma</i> -specific IgE and IgG in combination D/praziquantel group compared to praziquantel alone No difference in urine egg counts in D group at 3 weeks compared to placebo Significant drop in urine egg counts in groups receiving praziquantel alone or in combination, compared to D group or placebo group

PC=placebo controlled, R = randomized, CT = clinical trial, NR = not reported