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VITAMIN D FOR TREATMENT AND PREVENTION Of INFECTIOUS DISEASES: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Objective—To 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 on the basis of the evidence reviewed.

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

Results—Thirteen published controlled trials were identified by our search criteria. Ten trials were placebo controlled, and 9 of the 10 were conducted in a rigorous double-blind design. The selected clinical trials demonstrated substantial heterogeneity in baseline patient demographics, sample size, and vitamin D intervention strategies. Serious adverse events attributable to vitamin D supplementation were rare across all studies. On the basis of studies reviewed to date, the strongest evidence supports further research into adjunctive vitamin D therapy for tuberculosis, influenza, and viral upper respiratory tract illnesses. In the selected studies, certain aspects of study design are highlighted to help guide future clinical research in the field.

Conclusion—More rigorously designed clinical trials are needed for further evaluation of the relationship between vitamin D status and the immune response to infection as well as for delineation of necessary changes in clinical practice and medical care of patients with vitamin D deficiency in infectious disease settings.

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DISCLOSURE

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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 D_3 from cod liver oil, which was used to treat tuberculosis (TB) in the 1930s, led to its widespread use in TB treatment and prevention, until the introduction of antiinfective chemotherapy in the 1950s (2). More recently, epidemiologic studies have demonstrated strong associations between seasonal variations in vitamin D levels and the incidence of various infectious diseases, including septic shock (3), respiratory infection (4), and influenza (4,5).

Our understanding of vitamin D metabolism and its extraskeletal functions has improved considerably during the past 3 decades. The discovery that vitamin D receptor (VDR) and 1α-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. Moreover, the discovery of nonskeletal functions of vitamin D has reinvigorated interest in vitamin D as a potential modulator in a variety of disease states (8–10). Recent studies have demonstrated that vitamin D regulates the expression of specific endogenous antimicrobial peptides in immune cells (11); this action leads to a potential role for vitamin D in modulating the immune response to various infectious diseases.

These findings highlight the need to refine our understanding of the nonskeletal functions of vitamin D through future controlled studies of vitamin D supplementation and clinical outcomes in specific disease states. In this report, 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 by Rook et al (12) and Crowle et al (13) in the 1980s demonstrated that vitamin D enhanced bactericidal activity of human macrophages against *Mycobacterium tuberculosis*, the causative agent of TB. 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 et al (11) provided a key mechanism to how vitamin D may enhance innate immunity. This group demonstrated that stimulation of macrophage-bound Toll-like receptor 2/1 complex by *M tuberculosis*-derived antigens upregulates the expression of both VDR and CYP27b1, an enzyme that converts 25-hydroxyvitamin D (25-OHD) to its active 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D] form. Intracellular 1,25-$(OH)_2$D generated though action of CYP27b1 then interacts with the VDR and leads to induction of the antimicrobial peptide cathelicidin and killing of intracellular *M tuberculosis* (11). In the state of vitamin D deficiency, the infected macrophage is unable to produce sufficient 1,25-$(OH)_2$D to upregulate production of cathelicidin.

Although this antimicrobial mechanism of vitamin D has been demonstrated only in macrophages infected with *M tuberculosis*, 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. Endoscopic studies in humans have demonstrated that β-defensin is secreted in the gastric mucosa after 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 cause upregulation of the oxidative burst in activated macrophages (17), thus augmenting another multipurpose 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 tuberculosis* (18,19). Therefore, much of what we learn from the interaction between host vitamin D status and TB infection can enhance our understanding about 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 tract 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 major contributor to seasonal variations in human mortality (21). On the basis of these observations, Cannell et al (5) have argued that vitamin D status may be a contributor in determining the population susceptibility to seasonal epidemic outbreaks as well as the degree of associated morbidity and mortality, 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 the 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 proinflammatory cytokines, such as tumor necrosis factor α and interleukin-12, and 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 have a major role in the immune defense of the respiratory system through direct inactivation of viral pathogens (25) and increased recruitment of phagocytes (26). Collectively, 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 downregulating overly exuberant (and thus toxic) cytokine responses, while allowing for improved clearance of various microbial species (5).

The relationship between vitamin D status and human immunodeficiency virus (HIV) infection is also capturing more attention in recent literature. At this point, it is uncertain whether vitamin D status is associated with particular outcomes of HIV-related disease and potential for immunologic recovery with antiretroviral therapy. Recent studies, however, do suggest that there may be an increased prevalence of vitamin D deficiency in HIV-infected patients in comparison with uninfected hosts, although these data remain conflicting (27,28). Laboratory models of HIV infection have demonstrated that pretreatment of human monocytes and macrophages with 1,25-$(OH)_2$D prevents HIV infection in certain cell lines (29), while increasing HIV replication in others (30). Another recent study demonstrated that cathelicidin, the antimicrobial peptide regulated in part by vitamin D, may directly inhibit replication of HIV (31). Therefore, the relationship among vitamin D metabolism, HIV disease, and HIV therapy appears complex, and additional 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 the vitamin D status of the host may affect the overall bias of the host immune response, in which vitamin D repletion appears to favor a Th2-based cytokine profile that 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 (32,33). These findings, however, appear counterintuitive to what is known about vitamin D-mediated effects on immune responses to intracellular pathogens such as *M tuberculosis*, in which effective Th1-driven granuloma formation favors containment of latent TB infection and prevention of progression to active TB disease (34). Therefore, more information is needed to help understand the balance among cytokine responses, host vitamin D status, and subsequent host-pathogen interactions with regard 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 through 2009, using combinations of search terms including the following: "vitamin D_2, ergocalciferol, vitamin D_3, 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 (35–47) (Table 1). Ten trials were placebo controlled (35–37,40,42–47), and 9 of the 10 were conducted in a double-blind design. Five of the 13 trials (35–39) addressed vitamin D supplementation in patients with bacterial infection, with 4 of the 5 trials evaluating vitamin D as adjunctive therapy in patients with various forms of TB infection. Seven trials (40–45,47) were predominantly focused on vitamin D in subjects with viral infections, and 1 trial (46) was conducted in subjects with schistosomiasis, a helminth infection.

The selected clinical trials demonstrated considerable heterogeneity in baseline patient demographics, sample size, and vitamin D intervention strategies. Four of the 13 trials were conducted in pediatric populations (38,41,45,46), whereas 3 other trials were in either postmenopausal (42) or elderly patients (39,43). Sample size ranged from 24 subjects in a pediatric TB trial (38) to 3,444 subjects participating in a study of vitamin D and infection in elderly persons (43). Comorbid conditions also varied among the study populations, with inclusion of some HIV-infected patients in a large TB treatment trial (35) and 1 study being conducted exclusively in patients receiving hemodialysis (40).

Seven of the 13 trials specified whether ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) was used (35,36,39,42,43,45,47); cholecalciferol was favored over ergocalciferol in all but 1 study (36). Vitamin D replacement strategies varied in frequency and dose of therapy, ranging from 40 IU of vitamin D_3 given daily for 20 years to 100,000 IU of vitamin D_3 given bimonthly for 12 months (Table 2,Table 3, and Table 4). Three studies used high-dose vitamin D repletion regimens, such as 3 doses of 100,000 IU given during an interval of 8 months (35), 60,000 IU administered weekly for 6 weeks (41), or 600,000 IU given during a 12-month period (45). Two (35,45) of the 3 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 notably,

and our analysis of study outcomes (Table 1) revealed no clear trend toward positive study results favoring either long-term daily repletion or bolus replacement.

Six of the 13 clinical trials (35,36,38,42,45,47) provided information regarding the effectiveness of their selected repletion strategy by reporting baseline and follow-up 25-OHD or 1,25-$(OH)_2$D levels in the intervention group in comparison with control or placebo groups (Table 2,Table 3, and Table 4). Eleven of the 13 studies enrolled patients irrespective of baseline vitamin D status. In contrast, 1 study included only patients with a baseline 1,25-$(OH)_2$D level below the reference range (40), and another study excluded patients with evidence of severe vitamin D deficiency, defined as a baseline serum 25-OHD level <12 ng/mL (45). Of note, serious adverse events, such as clinically relevant hypercalcemia as a result of vitamin D supplementation, were rare across all studies. Two of the 13 trials (40,42) reported instances of hypercalcemia in a total of 3 study subjects, necessitating a 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 5 studies were conducted in TB-infected patients and yielded mixed results. Although the outcome of a translational study done by Martineau et al (36) was encouraging, inasmuch as administration of a single dose of 100,000 IU of ergocalciferol to purified protein derivative-positive contacts of active TB cases improved their immunologic control of bacille Calmette-Guérin (an *M tuberculosis* surrogate) in the peripheral blood, other trials focusing on clinical end points related to TB treatment have generated conflicting results (35,37,38). Two of the 3 clinical TB studies, by Morcos et al (38) and Nursyam et al (37) (Table 2), demonstrated a positive outcome. Morcos et al (38) reported a benefit of increased weight gain and faster resolution of TB symptoms in children treated with 1,000 IU of vitamin D daily as an adjunct to standard TB therapy. Nursyam et al (37) demonstrated significantly higher rates of sputum conversion to culture negativity in the group treated with 10,000 IU of vitamin D daily for 6 weeks in comparison with placebo. Both studies, however, failed to report baseline or follow-up serum 25-OHD levels for either the intervention or the control group, leaving uncertainty about the adequacy of repletion in each case. Although Morcos et al (38) did report 1,25-$(OH)_2$D levels before and after vitamin D treatment (Table 2), these may not provide an adequate refection of overall vitamin D status of the study subjects (48).

In contrast, a 2009 trial of vitamin D therapy in patients with TB reported by Wejse (35) found a significant increase in serum 25-OHD levels in the intervention group receiving 100,000 IU of vitamin D at baseline, 5 months, and 8 months of TB therapy. The author reported that levels of 25-OHD increased from 31 ng/mL at baseline to 41 ng/ mL and 39 ng/mL at 2 and 8 months of follow-up, respectively. Perhaps surprisingly, however, similar 25-OHD levels were reported at baseline, 2 months, and 8 months in the placebo group (35) (Table 2); this observation suggests that the vitamin D dose given to the intervention group was not sufficient to increase 25-OHD levels beyond what would be noted with TB treatment alone. Hence, interpretation of the data is 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 found no difference in TB-related clinical outcomes between the 2 study groups (35). Recruitment and follow-up for the study took place during the course of 24 months, and it is unclear whether seasonal alterations in vitamin D status affected any study outcomes (35).

In the last trial included in Table 2, Kawaura (39) reported a 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 for 2 decades versus control subjects receiving no

supplement. Although the study is hypothesis-generating for future investigations 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 group.

Therefore, the currently available data from studies in humans regarding the potential value of vitamin D as adjunctive therapy in bacterial infection remain conflicting. Three of the 4 TB trials, and the 1 trial of vitamin D therapy to prevent *H pylori*-related gastrointestinal disease, demonstrated positive outcomes, although these studies were hampered by major 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, reported by Wejse (35), demonstrated no clear benefit of adjunctive vitamin D therapy in TB treatment. As discussed in the foregoing material, vitamin D administered at doses higher than the total of 300,000 IU given to the intervention group in this study, along with careful attention to potential confounding factors 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 for further evaluation of the relationship between adequate vitamin D repletion and treatment or prevention (or both) of bacterial infections such as TB.

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 trials in humans have been performed to help translate these data into potential clinical applications. Our search identified 7 controlled trials concerning outcomes related to human viral infections (Table 3).

Vitamin D and Upper Respiratory Tract Viral Infections

Four of the 7 aforementioned studies evaluated the frequency of respiratory tract infection or influenza in vitamin D-treated patients in comparison with control subjects (41–43,47). An early trial by Rehman (41) most closely resembles a case-control study; 27 children were selected on the basis of a clinical history of recurrent respiratory or antibiotic-requiring illness and paired with age-matched control subjects documented to be free of recurrent infection. Subsequent analysis revealed the recurrent illness group to have a much higher prevalence of subclinical rickets (that is, pediatric vitamin D deficiency) and decreased recurrence of respiratory infection after a course of aggressive vitamin D repletion, given as 60,000 IU weekly for 6 weeks (41). Despite its promising results, however, the study is subject to several pitfalls, including absence of a placebo control arm, limited sample size, and limited documentation regarding effectiveness of the chosen vitamin D repletion regimen (Table 3), which may affect the generalizability and overall interpretation of the results.

The remaining 3 studies designed to evaluate the effect of vitamin D therapy in viral upper respiratory tract infection (URI) 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 (43) included a large sample size of 3,444 community-dwelling elderly subjects who were given 800 IU of vitamin D or placebo for longer than 2 years, as part of the Randomised Evaluation of Calcium or Vitamin D (RECORD) trial (49). This study failed to show a significant difference between the vitamin D and placebo groups in either the primary end point of fracture prevention or the secondary end point of self-reported infection rate in the week before assessment (43) (Table 3). The results of the RECORD study, however, are complicated by poor observed compliance with supplements in the study population, with only 54.5% of study subjects remaining compliant with study medication at 24 months of follow-up (43). Another trial, by Aloia and Li-Ng (42), included 208 healthy postmenopausal African American women who were given 800 IU of vitamin D daily or placebo for 2 years, followed

by 2,000 IU of vitamin D daily or placebo for 12 months. Although the primary outcome of bone mineral density in the original study (50) demonstrated no significant difference between the 2 groups, a lower rate of self-reported URI or influenza was observed in the intervention arm in comparison with the placebo group, and this effect was further magnified with an increase in the vitamin D dosage from 800 IU daily to 2,000 IU daily (42). Of note, in contrast to the study by Avenell et al (43), which demonstrated relatively meager increases in serum 25-OHD levels of the intervention group after vitamin D therapy (Table 3), the trial by Aloia and Li-Ng (42) reported follow-up mean serum 25-OHD levels commensurate with the current definition of vitamin D sufficiency at levels of 25-OHD ≥32 ng/mL (48). This difference in study design highlights the putative importance of ensuring adequate vitamin D repletion (at least >30 to 32 ng/mL) to maximize its extraskeletal and immunomodulatory effects in future intervention trials.

A recently published dedicated follow-up study by Li-Ng et al (47), however, in which 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 2 primary outcomes—the incidence and the severity of URI symptoms—for the vitamin D group versus the placebo group. This lack of significant difference in outcome was noted despite appropriate increases in serum 25-OHD 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 emphasized that although no major benefit of prevention of URI was observed in this study, the statistical trend appeared to favor the vitamin D-receiving group. This finding suggests that a larger sample size and more robust vitamin D repletion, perhaps for a longer period, may be beneficial in the design of future studies.

Vitamin D and Vaccination

Two additional studies evaluated the role of vitamin D as adjuvant therapy to boost hepatitis B (40) and influenza vaccine responses (44) as a novel approach to using vitamin D as preventive therapy for viral infection. Moe et al (40) treated 31 hemodialysis patients with the vitamin D analogue paricalcitol for 12 weeks (Table 3) in an effort to improve the blunted immunogenicity profile of hepatitis B vaccine seen in patients with end-stage renal disease and hemodialysis (51). Similarly, Kriesel and Spruance (44) administered single intramuscular doses of 40 IU of vitamin D or saline placebo to attempt to boost immune responses after influenza vaccination in 175 healthy volunteers. Neither study demonstrated a significant increase in hepatitis B or hemagglutination titers in the intervention group in comparison with the placebo group (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-$(OH)_2$D levels and the rate of CD4 count decline and HIV-related mortality (52), few prospectively designed clinical studies have been done to determine any causal relationship among host vitamin D status, immunologic decline, and clinical outcomes in HIV-seropositive patients. Some large studies of multivitamin and micronutrient formulations containing modest doses of vitamin D have demonstrated decreases in morbidity and mortality when given to HIV-positive patients in developing countries, especially those concurrently infected with *M tuberculosis* (53,54), but it is difficult to extrapolate any vitamin D-specific effects from these data.

Our search criteria identified 1 recent randomized placebo-controlled trial of isolated vitamin D therapy in a pediatric HIV-positive population. Arpadi et al (45) reported administering

100,000 IU of cholecalciferol or placebo bimonthly during a period of 12 months to 56 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 study subjects in the vitamin D group were documented to have 25-OHD levels of 30 ng/mL or higher at the end of the study follow-up, the study did not demonstrate a statistically significant difference between the 2 groups in gains in CD4 count or improvements in virologic control (45). Because of the potential antagonistic relationship between antiretroviral therapy and vitamin D metabolism, particularly its effect on 1,25-$(OH)_2$D, rather than 25-OHD levels, as suggested by the literature, future trials in this area may benefit from a study design that includes a larger study population, more aggressive vitamin D dosing to achieve levels of 25-OHD considered optimal, and stratification on the basis of the subjects' antiretroviral regimen. These steps may help to delineate nuances of the complex immunologic 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 performed to help illustrate the full therapeutic potential of vitamin D as an adjunctive or preventive strategy in these settings. Initial promising results from studies evaluating the prevalence of viral URI and influenza in vitamin D-treated subjects can be informative for future trials in this field. Additional information from both clinical and laboratory-driven studies is clearly needed to help elucidate the complex interplay among vitamin D status, vitamin D metabolism, and HIV infection in the human host.

Vitamin D and 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 1 such trial (Table 4), by Snyman et al (46), in which 59 adolescents received 40 IU of vitamin D or placebo daily for 5 days in a 2-by-2 factorial design with or without antiparasitic therapy for *Schistosoma haematobium* infection, a common parasitic illness in the developing world. The results of the study by Snyman et al (46) 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.

CONCLUSION

Recent studies have described a high prevalence of vitamin D insufficiency and overt vitamin D deficiency in human populations worldwide (48). As our knowledge of the extraskeletal functions of vitamin D continues to grow, the clinical significance of maintaining vitamin D sufficiency becomes more apparent. Several of the studies reviewed in this report build on existing preclinical research in vitamin D immunology, which demonstrates a likely connection among vitamin D repletion, susceptibility to infection, and clinical outcomes in a variety of infectious processes. On the basis of 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 tract illnesses. Some of the studies we discussed also included nonspecific outcomes, demonstrating that adequate vitamin D status may decrease all-cause infection rates in the populations analyzed (40,41,43). Although these investigations yielded mixed results (40,43), future population-based studies to evaluate broad effects of vitamin D supplementation on infection rates and total mortality may be warranted.

Collectively, the results of the studies discussed in this report highlight the need for more research for further characterization of the complex interplay among vitamin D deficiency, vitamin D repletion, and host response to infectious diseases, as well as for extraction of

specific, clinically relevant effects of vitamin D repletion in these settings. As a 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 for infectious diseases. First, the therapeutic potential of vitamin D-based interventions can be assessed only if there is adequate documentation of the effectiveness of the selected repletion regimen in terms of improving the vitamin D status of the host—that is, an increase in serum 25-OHD levels. Therefore, measurement and reporting of prerepletion and postrepletion serum 25-OHD levels must be an essential component of future studies in this field. Second, recent strides toward defining "vitamin D sufficiency" as a serum 25-OHD level >30 to 32 ng/mL (48) create a good target to frame future studies of vitamin D supplementation and to standardize vitamin D repletion protocols. The immunomodulatory and antimicrobial effects of vitamin D, however, may require higher serum 25-OHD levels, thus necessitating more aggressive dosing schemes, as suggested by the results of the TB treatment study conducted by Wejse (35) in Guinea-Bissau and the recent URI study conducted by Li-Ng et al (47). Therefore, dose-ranging studies may be necessary to establish repletion thresholds to guide further studies evaluating the extraskeletal 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 end points, may confound future prospective studies in the field of vitamin D immunology. Rigorous study design will be key in achieving 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.

Abbreviations

HIV	human immunodeficiency virus
1,25-$(OH)_2$D	1,25-dihydroxyvitamin D
25-OHD	25-hydroxyvitamin D
TB	tuberculosis
URI	upper respiratory tract infection
VDR	vitamin D receptor

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Table 1

Controlled Human Trials of Vitamin D Therapy for Infection Identified Through a Systematic Literature Search

Study pathogen (reference)	No. Of patients	Total vitamin D dose and duration	Results summary
Bacterial			
Mycobacterium tuberculosis			
Wejse (35), 2009	365	300,000 IU/8 mo	−−[a]
Martineau et al (36), 2007	131	100,000 IU once	++[b]
Nursyam et al (37), 2006	67	420,000 IU/6 wk	++[b]
Morcos et al (38), 1998	24	36,000 IU/2 mo	+[c]
Helicobacter pylori			
Kawaura (39), 2006	34	292,000 IU/20 y	++[b]
Viral			
Upper respiratory tract infection			
Rehman (41), 1994	27	360,000 IU/6 wk	++[b]
Aloia & Li-Ng (42), 2007	208	1,296,000 IU/36 mo	++[b]
Avenell et al (43), 2007	3,444	576,000 IU/24 mo	−−[a]
Li-Ng et al (47), 2009	162	168,000 IU/12 wk	−−[a]
Influenza			
Aloia & Li-Ng (42), 2007	208	1,296,000 IU/36 mo	++[b]
Immune responses to vaccines against viruses			
Hepatitis B vaccine			
Moe et al (40), 2001	31	144 μg paricalcitol/12 wk	−−[a]
Influenza vaccine			
Kriesel & Spruance (44), 1999	175	40 IU once	−−[a]
Human immunodeficiency virus			
Arpadi et al (45), 2009	56	600,000 IU/12 mo	−−[a]
Other			
Schistosoma haematobium			
Snyman et al (46), 1997	59	200 IU/5 d	+[c]

[a] No study end points met, negative study.

[b] All study end points met, positive study.

[c] Some study end points met, mixed results.

Table 2

Intervention Trials Evaluating Vitamin D Replacement as Treatment or Prevention of Bacterial Infection[a]

Reference, country, study type	Study population	Main end point(s)	Intervention	Mean serum vitamin D level		Outcome
				Baseline	Follow-up	
Wejse (35), 2009 Guinea-Buissau DB-PC-R-CT	365 adults with pulmonary TB n1 = 187 (23) n2 = 178 (19)	Sputum conversion rates over time Points on TB score clinical severity assessment tool 12-mo mortality Lymphocyte subsets	100,000 IU D3 or placebo given at baseline, 5 mo, and 8 mo of TB therapy	n1=31 ng/mL[b] n2 = 32 ng/mL[b]	n1 =41 ng/mL @ 2 mo,[b] 39 ng/mL @ 8 mo[b] n2 = 42 ng/mL @ 2 mo,[b] 41 ng/mL @ 8 mo[b]	No difference in sputum conversion, TB score 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 (36), 2007 South Africa DB-PC-R-CT	131 adult TB contacts n1=64(NR) n2 = 67 (NR)	Whole blood restriction of BCG-lux luminescence (a surrogate of Mtb) Whole blood interferon-γ release after stimulation by TB antigens	100,000 IU D2 or placebo given at baseline	n1=14 ng/mL[b] n2 = NR	n1 = 27 ng/mL @ 6 wk[b] n2 = NR	20.4% greater restriction of BCG-lux growth by blood from vitamin D group (P = .03) No observed difference in interferon-γ release between groups No adverse events observed
Nursyam et al (37), 2006 Indonesia DB-PC-R-CT	67 adults with smear-positive pulmonary TB n1=34 (NR) n2 = 33 (NR)	Sputum smear conversion at 6 wk Radiographic improvement	10,000 IU/d vitamin D or placebo given for first 6 wk of TB treatment	NR	NR	23% greater sputum conversion rate at 6 wk in vitamin D group versus placebo (P = .002) 22.5% greater rate of radiographic improvement in vitamin D group versus placebo (P = NR)
Morcos et al (38), 1998 Egypt R-CT	24 children (1.5–13 y) 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/d vitamin D given in combination with standard TB therapy, or TB therapy alone	17.91 pg/mL for both groups[c]	n1 = 24.09 pg/mL[c] n2 = 20.83 pg/mL[c]	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<.005)
Kawaura (39), 2006 Japan CT	34 female nursing home residents (70–99 y) with or without osteopenia n1 = 15 (NR) n2 = 19 (NR)	Serum pepsinogen and gastrin levels Rate of *H pylori* infection by serology	40 IU/d D3 given over 20 y for diagnosis of osteopenia or no supplement in nonosteopenic control subjects	NR	NR	Lower mean serum pepsinogen level in vitamin D arm (P<.05) Lower rates of positive *H pylori* serology in vitamin D group (P<.05)

[a] BCG = bacille Calmette-Guérin; CT = clinical trial; D2 = ergocalciferol; D3 = cholecalciferol; DB = double-blind; HIV = human immunodeficiency virus; *H pylori* = *Helicobacter pylori;* Mtb = *Mycobacterium tuberculosis*; n1 = intervention (% HIV+); n2 = placebo (% HIV+); NR = not reported; PC = placebo-controlled; R = randomized; TB = tuberculosis.

[b] Serum 25-hydroxyvitamin D

[c] Serum 1,25-dihydroxyvitamin D.

Table 3

Intervention Trials Evaluating Vitamin D as Treatment or Prevention of Viral Infection[a]

Reference, country, study type	Study population	Main end point(s)	Intervention	Mean serum vitamin D level		Outcome
				Baseline	Follow-up	
Moe et al (40), 2001 United States DB-PC-R-CT	31 hemodialysis patients with low PTH levels not otherwise on vitamin D therapy n1 = 16 (NR) n2 = 15 (NR)	DHT anergy to PPD, mumps, *Candida*, *Trichophyton* at BL and 12 wk PBMC proliferative responses at BL and 12 wk PBMC cytokine production at BL and 12 wk Antibody titer in response to hepatitis B vaccine at 8 wk Number of infections accessed by no. of antibiotic prescriptions	4 μg paricalcitol intravenously 3 times weekly during dialysis for 12 wk or placebo	NR	NR	Higher rate of conversion from anergic to reactive skin test in paricalcitol group, although difference not statistically significant (P = .09) No observed differences in PBMC proliferative or cytokine responses between groups No observed difference in antibody titers after vaccination with hepatitis B vaccine No observed difference in infection between groups Paricalcitol group experienced more hypercalcemic events, although difference was not significant
Rehman (41), 1994 India CT	27 children (3–12 y) with ≥6 respiratory or antibiotic-requiring illnesses in prior 6 mo and 20 children (3–12 y) with ≤1 respiratory or antibiotic-requiring illness in prior 6 mo; HIV status NR	Elevated serum alkaline phosphatase as proxy for diagnosis of subclinical rickets Frequency of respiratory infection in 6 mo after intervention	60,000 IU vitamin D weekly × 6 wk 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<.005) versus control Difference in infection rates between groups no longer significant in 6 mo after intervention (P = NR)
Aloia & Li-Ng (42), 2007 United States DB-PC-R-CT	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 influenza events	800 IU/d D3 for 24 mo followed by 2,000 IU D3 daily for 12 mo, or placebo for 36 mo	n1 = 18.8 ng/mL[b] n2 = 17.2 ng/mL[b]	n1 =28.4 ng/mL @ 3 mo of 800 IU D3, 34.8 ng/mL @ 3 mo of 2,000 IU D3[b] n2 = NR	Lower rate of reported URI symptoms in intervention group versus placebo (P<.002) Placebo group more likely to experience symptoms in winter versus intervention group (P = NR) Lower rate of reported URI symptoms while receiving 2,000 IU D3 per day versus 800 IU D3 per day (P = NR)
Avenell et al (43), 2007 England DB-PC-R-CT	3,444 elderly subjects participating in RECORD trial who also responded to a follow-up questionnaire n1 = 1,740 (NR) n2= 1,704 (NR)	Self-report of infection or antibiotic-requiring illness during the week preceding receipt of questionnaire in mail	800 IU/d D3 for 24–62 mo, or placebo	15.2 ng/mL[b] in subsample of 60 patients selected across all groups	n2 = 24.9 ng/mL[b] mean in subsample of 60 patients selected from vitamin D group	No difference in self-report of illness or antibiotic prescriptions between groups (P = .23 and .18, respectively)
Li-Ng et al (47), 2009 United States DB-PC-R-CT	162 healthy adult outpatients n1=84 (0) n2 = 78 (0)	Self-report of URI symptoms Self-report of URI symptom severity	2,000 IU/d D3 for 12 wk, or placebo	n1 = 25.72 ng/mL[b] n2 = 25.2 ng/mL[b]	n1=35.4 ng/mL[b] n2 = 24.4 ng/mL[b]	No difference in frequency (P = .56), severity (P = .4), or duration (P = .86) of URIs incurred by both groups during study period, but statistical trend noted to favor vitamin D group in all outcomes
Kriesel & Spruance (44), 1999	175 healthy volunteers receiving killed influenza	Hemagglutination titers against	40 IU vitamin D IM × 1 dose or	NR	NR	No difference in hemagglutination titers at 28 or 90 days after vaccination between groups

Reference, country, study type	Study population	Main end point(s)	Intervention	Mean serum vitamin D level		Outcome
				Baseline	Follow-up	
United States DB-PC-R-CT	vaccination n1= 87 (NR) n2 = 88 (NR)	H1N1,H3N2, and influenza B	saline placebo IM, administered with influenza vaccine			
Arpadi et al (45), 2009 United States DB-PC-R-CT	56 HIV-infected children and adolescents n1=29(100%) n2 = 27(100%)	Change in CD4 count and viral load during 12-mo study follow-up Hypercalcemia	100,000 IU D3 bimonthly for 12 mo, or placebo	n1=24.1 ng/mL[b] n2 = 23.6 ng/mL[b]	n1 =32.4 ng/mL @ 12 mo[b] n2 = 21.9 ng/mL @ 12 mo[b]	No difference in change in CD4 count and viral load between groups at 12 mo No episodes of hypercalcemia

[a] BL = baseline; CT = clinical trial; D3 = cholecalciferol; DB = double-blind; DHT = delayed hypersensitivity testing; HIV = human immunodeficiency virus; IM = intramuscularly; n1 = intervention (% HIV +); n2 = placebo (% HIV+); NR = not reported; PBMC = peripheral blood mononuclear cells; PC = placebo-controlled; PPD = purified protein derivative; PTH = parathyroid hormone; R = randomized; RECORD = Randomised Evaluation of Calcium or Vitamin D; URI = upper respiratory tract infection.

[b] Serum 25-hydroxyvitamin D.

Table 4

Intervention Trial Evaluating Vitamin D as Treatment or Prevention of Parasitic Infection[a]

Reference, country, study type	Study population	Main end point(s)	Intervention	Outcome[b]
Snyman et al (46), 1997 South Africa PC-R-CT	59 adolescents with *Schistosoma haematobium* infection n1 = 14 (D3) n2 = 16 (D3 + praziquantel) n3 = 14 (praziquantel) n4 = 15 (placebo) HIV status NR	Cell subtype counts in peripheral blood	40 IU vitamin D daily × 5 days given alone, or in combination with praziquantel × 1 dose, or praziquantel alone × 1 dose, or placebo	Increased vacuolated eosinophils in D3 group versus other 3 groups
		Eosinophil cationic protein level in peripheral blood		Decreased eosinophil cationic protein in D3 group versus other 3 groups
		Specific IgE and IgG for whole-worm antigen in peripheral blood		Higher titers of *Schistosoma*-specific IgE and IgG in combination D3 + praziquantel group versus praziquantel alone
		Egg shedding in the urine		No difference in urine egg counts in D3 group at 3 wk versus placebo
				Significant decline in urine egg counts in groups receiving praziquantel alone or in combination versus D3 group or placebo group

[a] CT = clinical trial; D3 = cholecalciferol; HIV = human immunodeficiency virus; NR = not reported; PC = placebo-controlled; R = randomized

[b] Mean serum vitamin D levels at baseline and follow-up were not reported.