Vitamin D status, 1,25-dihydroxyvitamin D_3, and the immune system[1–4]

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ABSTRACT

Vitamin D is an important immune system regulator. The active form of vitamin D, 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], has been shown to inhibit the development of autoimmune diseases, including inflammatory bowel disease (IBD). Paradoxically, other immune system-mediated diseases (experimental asthma) and immunity to infectious organisms were unaffected by 1,25$(OH)_2D_3$ treatment. There are similar paradoxical effects of vitamin D deficiency on various immune system functions. Vitamin D and vitamin D receptor (VDR) deficiency resulted in accelerated IBD. Experimental asthma was unaffected by 1,25$(OH)_2D_3$ treatment and was less severe among VDR-deficient mice. Vitamin D is a selective regulator of the immune system, and the outcome of 1,25$(OH)_2D_3$ treatment, vitamin D deficiency, or VDR deficiency depends on the nature of the immune response (eg, infectious disease, asthma, or autoimmune disease). An additional factor that determines the effect of vitamin D status on immune function is dietary calcium. Dietary calcium has independent effects on IBD severity. Vitamin D-deficient mice on low-calcium diets developed the most severe IBD, and 1,25$(OH)_2D_3$ treatment of mice on low-calcium diets improved IBD symptoms. However, the best results for IBD were observed when the calcium concentration was high and 1,25$(OH)_2D_3$ was administered. Both the type of immune response and the calcium status of the host determine the effects of vitamin D status and 1,25$(OH)_2D_3$ on immunity. *Am J Clin Nutr* 2004;80(suppl):1717S–20S.

KEY WORDS Vitamin D, vitamin D receptor, calcium, inflammation, mice

INTRODUCTION

The classic function of vitamin D is to regulate calcium homeostasis and thus bone formation and resorption. However, less-traditional functions of vitamin D have been demonstrated and include effects on the immune response. The identification of vitamin D receptors (VDRs) in peripheral blood mononuclear cells sparked the early interest in vitamin D as an immune system regulator (1, 2). Vitamin D deficiency has been linked to several different diseases, including the immune system-mediated diseases ulcerative colitis and Crohn's disease.

INFLAMMATORY BOWEL DISEASES AND VITAMIN D STATUS

A major source of vitamin D is its manufacture through a photolysis reaction in the skin; vitamin D available from sunlight exposure is significantly less in northern climates, and concentrations are especially low during the winter (3, 4). In addition, dietary intake of vitamin D is problematic, because there are few foods that are naturally rich in vitamin D. Weight loss occurs for 65–75% of patients diagnosed as having Crohn's disease and 18–62% of patients with ulcerative colitis (5, 6). Vitamin deficiencies in general and vitamin D deficiency in particular have been shown to occur among patients with inflammatory bowel disease (IBD) (7).

Vitamin D deficiency is common among patients with Crohn's disease, even when the disease is in remission (7, 8). It is unclear why vitamin D deficiency occurs more frequently in IBD; it is probably attributable to the combined effects of low vitamin D intake, malabsorption of many nutrients including vitamin D, and decreased outdoor activities in climates that are not optimal for vitamin D synthesis in the skin. The standard treatments for patients with IBD include short-term high-dose and long-term low-dose prednisone therapy (8–10). Prednisone and other corticosteroid therapies result in decreased bone mineral density, which increases the risks for vertebral fractures. Vitamin D deficiency has been linked to bone loss among patients with IBD, and bone loss is a problem for up to 50% of patients with IBD (7, 8). A placebo-controlled study showed that calcium and vitamin D supplementation were effective for preventing bone loss among patients with Crohn's disease (7, 8, 11). The hormonally active form of vitamin D, 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], is known to increase bone mineralization when administered to experimental animals (12) and human subjects (13). Therefore, vitamin D and/or 1,25$(OH)_2D_3$ supplementation is warranted for patients with IBD, to maintain bone mineral density and to normalize circulating vitamin D concentrations.

HELPER T CELLS

Helper T (Th) cells are central to all antigen-specific immune responses. The microenvironment in which naive Th cells develop determines which of 2 subtypes predominates (Th1 or Th2)

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(reviewed in ref 14). The Th1 and Th2 cell responses regulate each other and, during "normal" immune responses, the host responds with a balance of the 2 subtypes. Th1 cells secrete interferon γ (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor α. Th1 cell activation is essential for strong cell-mediated immune responses, including host responses to tumors and intracellular pathogens (such as viruses). In autoimmune diseases, Th1 cells are misdirected against self proteins, which results in pathologic conditions. Examples of these Th1 cell-driven diseases include multiple sclerosis, type 1 diabetes mellitus, and IBD. Th2 cells secrete IL-4 and IL-5, both of which are important for strong antibody-mediated immunity. Host responses to extracellular pathogens (most bacteria and parasites) require Th2 cells. Allergies and asthma are diseases driven by Th2 cells, and they occur when the immune system responds to different environmental antigens. The balance in Th cell responses dictates the outcome of any given challenge to the immune system. Some outcomes are beneficial (clearance of infections), and some are detrimental (autoimmunity and asthma).

Th1 and Th2 cells are direct targets of $1,25(OH)_2D_3$. Quiescent $CD4^+$ T cells expressed VDRs but only at low concentrations, which increased 5-fold after activation (15). $1,25(OH)_2D_3$ decreased the proliferation of purified Th cells and decreased the production of IFN-γ, IL-2, and IL-5 (15). In Th2 cells, $1,25(OH)_2D_3$ increased the production of IL-4 (15). The effectiveness of $1,25(OH)_2D_3$ for suppression of autoimmune diseases in vivo has been shown to depend on IL-2 (16) and IL-4 (17) secretion. $CD4^+$ T cells from VDR knockout (KO) mice (which do not respond to vitamin D) produced more IFN-γ and less IL-2, IL-4, and IL-5 than did $CD4^+$ T cells from wild-type (WT) mice (18). Consistent with this finding, in vivo antigen stimulation of VDR KO mice resulted in increased antigen-specific IFN-γ response (18). Furthermore the mixed lymphocyte reaction with $CD4^+$ T cells from VDR KO mice was twice that with $CD4^+$ T cells from WT mice (18). The data suggest that T cells from VDR KO mice secrete more IFN-γ and less of the Th2 cytokines IL-4 and IL-5. Furthermore, $1,25(OH)_2D_3$ reduced Th1 cell-associated cytokine production and increased Th2 cell IL-4 secretion. In the absence of vitamin D signaling, the T cell compartment has a potentially stronger Th1 phenotype.

VITAMIN D AND EXPERIMENTAL IBD

In IBD, the immune system-mediated attack is against the gastrointestinal tract (9, 10). T cells that preferentially produced the Th1 cytokines (IL-2, IFN-γ, and tumor necrosis factor α) were shown to transfer Crohn's disease-like symptoms to naive mice (19, 20), and the production of Th1 cytokines is associated with IBD among humans subjects (21). In conventional animal facilities, IL-10 KO mice develop enterocolitis within 9–12 wk of life (22). Approximately 30% of IL-10 KO mice die after the development of severe anemia and weight loss (22).

Vitamin D deficiency accelerated the development of IBD symptoms among IL-10 KO mice (23). Vitamin D-deficient IL-10 KO mice began to die at 6 wk of life; by 9 wk of age, ~50% of the vitamin D-deficient IL-10 KO mice had succumbed to a wasting disease that was confirmed as IBD in the necropsy (**Figure 1**) (23). Vitamin D-sufficient IL-10 KO mice remained without symptoms until $\geq$ 12 wk of age (Figure 1). VDR/IL-10 double-KO mice developed severe colitis (rectal bleeding) beginning as early as 3 wk of age. By 5 wk of age, the double-KO

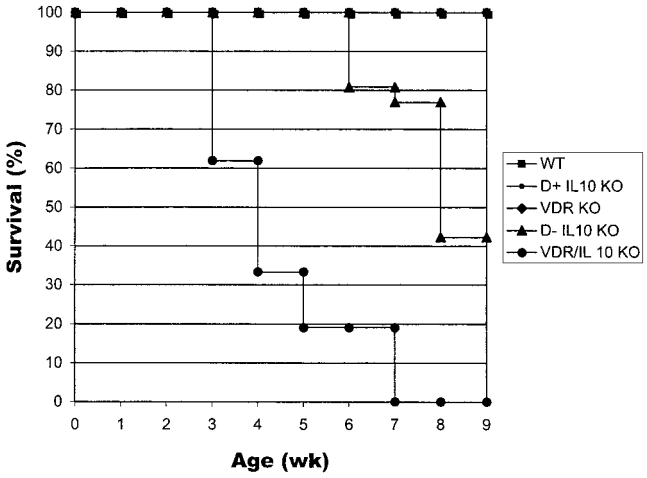

FIGURE 1. Vitamin D and VDR deficiency result in accelerated death of IL-10 KO mice. All mice were C57BL/6 mice. D+ IL-10 KO, vitamin D-sufficient IL-10 KO; D− IL-10 KO, vitamin D-deficient IL-10 KO; VDR/IL-10 KO, VDR/IL-10 double-KO. The premature death of the vitamin D-deficient IL-10 KO and VDR/IL-10 KO mice occurred after weight loss, rectal bleeding, prolapse of the colon, and microscopic evidence of severe inflammation of the small intestine and colon. The WT, vitamin D-sufficient IL-10 KO, and VDR KO mice all survived (100% survival) for the 9 wk; therefore, all 3 symbols overlap and are not discernible.

mice weighed 50% as much as their littermates and 67% as much as age-matched IL-10 KO mice (18). Macroscopically, the small intestine, cecum, and large intestine of VDR/IL-10 KO mice were enlarged, compared with VDR KO/IL-10 +/− littermates. All of the VDR/IL-10 KO mice were dead by 8 wk of age, compared with none of the VDR KO or IL-10 KO mice (Figure 1) (18). Rectal bleeding was apparent for all of the double-KO mice, and histopathologic sections of the colon demonstrated severe inflammation and epithelial hyperplasia (18).

When $CD4^+$ $CD45RB^{high}$ T cells from WT mice were injected into Rag KO (T and B cell-deficient) recipients, IBD symptoms developed ~12 wk later (19, 20, 24–27). The relative ability of VDR KO (versus WT) $CD4^+$ T cells to transfer IBD to the Rag KO mice (second experimental model of IBD) was assessed. Equal numbers of $CD4^+$ $CD45RB^{high}$ T cells were injected into Rag KO mice, the mice were maintained for 12 wk, and IBD severity was determined. Two of 7 VDR KO recipients and 1 of 7 WT recipients died as a result of severe colitis (18). The Rag KO mice that received the VDR KO $CD4^+$ $CD45RB^{high}$ T cells weighed the same (VDR KO: 17.4 $\pm$ 1.3 g; WT: 18.8 $\pm$ 1.2 g), had greater small intestine/body weight percentages (VDR KO: 11.0 $\pm$ 0.9%; WT: 6.8 $\pm$ 0.4%), had greater large intestine/body weight percentages (VDR KO: 6.4 $\pm$ 1.0%; WT: 3.6 $\pm$ 0.6%), and had higher histopathologic scores (VDR KO: 5.8 $\pm$ 0.5; WT: 2.9 $\pm$ 0.3) (18). The data showed that $CD4^+$ $CD45RB^{high}$ T cells from VDR KO mice increased the severity of IBD in the Rag KO mice, compared with similar cells from WT mice. VDR deficiency resulted in severe inflammation of the gastrointestinal tract in 2 experimental models of IBD (Th1 cell driven) (18).

VITAMIN D AND INFECTIOUS DISEASES

On the basis of the ability of $1,25(OH)_2D_3$ to suppress the development of various autoimmune diseases and to prolong

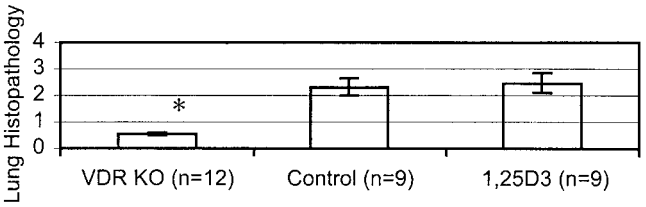

FIGURE 2. Experimental asthma fails to develop in VDR KO mice. Control, WT mice; $1,25D_3$, WT mice treated with 100 ng/d $1,25(OH)_2D_3$ for 2 wk. Experimental asthma was induced in all mice as described (34). Lungs from the mice were sectioned, stained, and scored blindly for inflammation and epithelial hyperplasia, as described (34). *VDR KO mice had significantly ($P < 0.05$) less lung pathologic evidence (inflammation and epithelial hyperplasia) than did control and $1,25(OH)_2D_3$-treated mice.

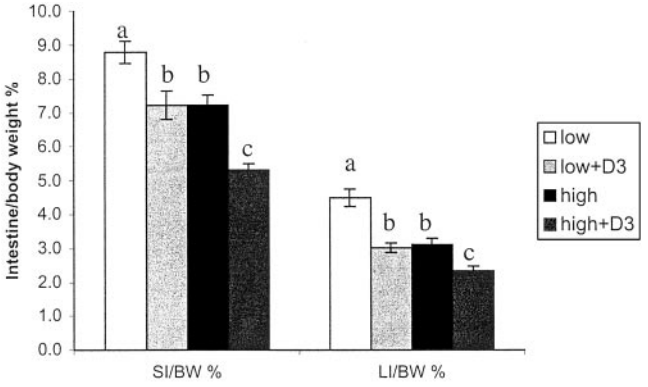

FIGURE 3. Both dietary calcium and $1,25(OH)_2D_3$ are important in experimental IBD. Vitamin D-deficient IL-10 KO mice were derived and maintained as described (23). At 5 wk, the diets of the vitamin D-deficient mice were either maintained with a high calcium concentration (2.2%) or switched to a low calcium concentration (0.2%). The groups were as follows: low, vitamin D-deficient IL-10 KO mice fed 0.2% calcium; low+D_3, vitamin D-deficient IL-10 KO mice fed 0.2% calcium and 20 ng/d $1,25(OH)_2D_3$; high, vitamin D-deficient IL-10 KO mice fed 2.2% calcium; high+D_3, vitamin D-deficient IL-10 KO mice fed 2.2% calcium and 20 ng/d $1,25(OH)_2D_3$. The mice were all killed 4 wk later, when the mice were 9 wk of age. SI/BW%, small intestine/body weight percentage; LI/BW%, large intestine/body weight percentage. The reported values are for 19-22 mice for each of the 4 treatment groups. Values with different letters are significantly different from each other ($P < 0.05$).

allograft survival, $1,25(OH)_2D_3$ has been called an immunosuppressive hormone (28, 29). However, $1,25(OH)_2D_3$ has been shown to have no effect on the susceptibility of mice to infections with herpes simplex virus or *Candida albicans* (12). The doses of $1,25(OH)_2D_3$ chosen were the same doses that had been shown previously to prolong allograft survival (12, 29). Surprisingly, little is known about the effect of vitamin D status on the ability of the host to fight infections. There is an interesting but mechanistically unsubstantiated link between vitamin D deficiency and cases of tuberculosis (30). Experimentally, vitamin D deficiency and host resistance to infectious diseases have not been studied extensively. One experiment in VDR KO mice showed that VDR KO mice exhibited increased granulomatous inflammation (slightly more severe infection) during *Schistosoma mansoni* infection, compared with WT mice (18). Little is known about the role of vitamin D and $1,25(OH)_2D_3$ in regulating immune responses to infectious diseases. What is known is somewhat paradoxical, on the basis of the ability of this nutrient/hormone to suppress autoimmune diseases and prolong transplant survival.

VITAMIN D AND EXPERIMENTAL ASTHMA

Asthma is a chronic inflammatory disease of the airways. In response to airborne allergens, the immune system of an asthmatic subject generates a strong cellular response in the lung airways. Th2 cell cytokine production, inflammation, and eosinophil infiltration result in increased production of mucus, epithelial cell thickening, and thus airway hyperresponsiveness. Experimental allergic asthma was induced in VDR KO, WT, and $1,25(OH)_2D_3$-treated WT mice. WT mice developed asthma, which was characterized by many inflammatory cells infiltrating the lungs. Lung histopathologic scores reflected the amount of epithelial hyperplasia and inflammation on a scale of 0 to 4 (maximum). The Th2 cell-driven disease experimental asthma failed to develop in VDR KO mice (**Figure 2**) (31). $1,25(OH)_2D_3$ treatment of WT control mice had no effect on asthma severity (Figure 2). VDR KO mice did develop antigen-specific Th2 cell responses in the periphery but failed to develop lung inflammation or airway hyperresponsiveness (31). The absence of vitamin D signaling through VDRs protected these mice from developing experimental asthma. The Th2 cell response does develop in the absence of VDRs; however, Th2 cells may not traffic to the lung and cause disease. It is also possible that epithelial cells in the lungs of VDR KO mice are unable to respond to an inflammatory challenge.

THE EFFECT OF VITAMIN D ON THE IMMUNE SYSTEM DEPENDS ON ADEQUATE CALCIUM

Vitamin D-deficient IL-10 KO mice were derived exactly as described (23). Vitamin D-deficient IL-10 KO mice were weaned at 5 wk of age and fed 1 of 4 diets for the subsequent 4 wk, as follows: vitamin D deficient with no added calcium (low calcium, 0.2% calcium), vitamin D deficient with high concentrations of calcium (high calcium, 2.2% calcium), $1,25(OH)_2D_3$ (20 ng/d) treated with no added calcium [low calcium plus $1,25(OH)_2D_3$], or $1,25(OH)_2D_3$ (20 ng/d) treated with high concentrations of calcium [high calcium plus $1,25(OH)_2D_3$]. Confirming the effectiveness of the diets, serum calcium concentrations were 1.3 ± 0.1 mmol/L for mice in the low calcium group, 2.0 ± 0.1 mmol/L for mice in the low calcium plus $1,25(OH)_2D_3$ group, 1.9 ± 0.1 mmol/L for mice in the high calcium group, and 2.6 ± 0.1 mmol/L for mice in the high calcium plus $1,25(OH)_2D_3$ group. We previously showed that small intestine/body weight percentage values are objective means for evaluating IBD susceptibility (23). Vitamin D-deficient IL-10 KO mice fed diets low in calcium had the largest small intestine and large intestine ratios (**Figure 3**). $1,25(OH)_2D_3$ treatment of mice on low-calcium diets was effective in reducing the small intestine/body weight percentage; however, the best result for IL-10 KO mice was with $1,25(OH)_2D_3$-containing diets that were also high in calcium (Figure 3) (23). IL-10 KO mice fed $1,25(OH)_2D_3$ and high-calcium diets had the same small intestine/body weight percentages as WT control animals (Figure 3) (23). The data for IL-10 KO mice confirmed previous data in a murine model of multiple sclerosis, which also showed that there were dietary calcium-dependent and -independent effects of $1,25(OH)_2D_3$ on autoimmune responses (32). Both dietary calcium and $1,25(OH)_2D_3$ are important regulators of autoimmune responses in the gastrointestinal tract and central nervous system.

TABLE 1
Vitamin D is a selective regulator of immunity[1]

Vitamin D treatment	Acute infection	IBD	Asthma
$1,25D_3$	+	−	+
Sufficient	+	+	+
Deficient	ND	++	ND
VDR KO	++	+++	−

[1] $1,25D_3$, $1,25(OH)_2D_3$-treated; sufficient, vitamin D-sufficient; deficient, vitamin D-deficient. The responses of vitamin D-sufficient hosts to acute infection, IBD, and asthma were set as the normal responses. All other responses were recorded relative to the vitamin D-sufficient response, (+, normal; ++, more severe; +++, extreme disease; −, little or no disease; ND, not done).

CONCLUSIONS

The in vivo effects of vitamin D status on immune function depend on the nature of the immune challenge (**Table 1**) and the calcium status of the host (Figure 3). Similarly, the direct targets of vitamin D in $CD4^+$ T cells depend on the timing and nature of the stimulation. Vitamin D- or VDR-deficient hosts have elevated Th1 cell-associated responses and decreased Th2 cell-associated responses. In the absence of VDRs, Th1 cell-driven IBD is more severe and Th2 cell-driven asthma does not develop. The evidence suggests a model in which the effectiveness of $1,25(OH)_2D_3$ treatment of autoimmune diseases results from inhibition of the development and function of Th1 cells and the induction of other Th cells, including Th2 cells (33). The availability of dietary calcium is a factor that contributes to the effectiveness of $1,25(OH)_2D_3$ as a treatment for IBD. The paradoxical effects of $1,25(OH)_2D_3$ on the ability of the host to mount an immune response to infectious microorganisms while suppressing autoimmune disease require additional investigation. It seems reasonable to hypothesize that vitamin D and $1,25(OH)_2D_3$ are selective regulators of the immune system, and additional work is needed to identify the cellular and molecular targets of $1,25(OH)_2D_3$ in the immune system.

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