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Vitamin D Levels in Adults with Crohn’s Disease Are Responsive to Disease Activity and Treatment

Maggie Ham, MD, Maria S. Longhi, MD, PhD, Conor Lahiff, MD, Adam Cheifetz, MD, Simon Robson, MD, PhD, and Alan C. Moss, MD

Division of Gastroenterology, Center for Inflammatory Bowel Disease, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Abstract

Background—Vitamin D deficiency is common in patients with Crohn’s disease (CD), although whether this impairs immune responsiveness, and is related to disease activity per se, remains unclear. We sought to investigate vitamin D pathways in patients with CD according to measures of inflammation and immune response.

Methods—Prospectively collected samples of a well-characterized cohort of patients with CD were used to measure serum 25(OH)-vitamin D levels by enzyme-linked immunoassay. Related gene expression was determined by polymerase chain reaction in T cells. The effect of vitamin D on the proliferation of isolated CD4⁺ cells was determined.

Results—Patients with active CD had lower serum vitamin D levels than those in clinical remission; this measurement was independent of season or reported use of vitamin D supplements. Harvey–Bradshaw Index scores, but not C-reactive protein, correlated with serum vitamin D levels. Gene expression of the vitamin D receptor was higher in peripheral blood T cells from patients with active disease than in those in remission. The proportion of CD25hi CD4⁺ cells from patients with CD increased in the presence of vitamin D. After treatment with infliximab, significant increases in serum vitamin D levels were noted in patients.

Conclusions—Low vitamin D levels are associated with disease activity in CD and increase after infliximab treatment.

Keywords

Crohn’s disease; vitamin D; infliximab

Vitamin D deficiency is common in patients with inflammatory bowel disease although it is not clear if this is cause or effect.^{1,2} Noted variations in Crohn’s disease (CD) prevalence and activity according to geographic latitude and seasons have been postulated to occur because of seasonal fluctuations in vitamin D levels.^{3,4} Epidemiological and clinical studies have associated serum vitamin D levels with the risk of developing CD and levels of disease

activity with established disease.^{5,6} Although these associations suggest causality, they have not been universally confirmed.^{7,8} However, a single trial of vitamin D was shown to decrease disease activity scores in a small cohort of patients with CD, suggesting therapeutic benefits from elevating vitamin D levels.⁹

Studies of vitamin D in patients with inflammatory bowel disease predominantly report serum levels of 25-hydroxyvitamin D (25(OH)D), an inactive precursor that circulates in the blood and has a half-life of 1 month.² Conversion of 25(OH) D to active 1 α ,25-dihydroxyvitamin D (1,25(OH)D) is performed by the enzyme CYP27B1, an enzyme now known to be expressed by many circulating immune cell types.^{10,11} The active 1,25(OH)D activates the vitamin D receptor (VDR), which eventually binds to VDR-response elements in the target cell's genome. Local production of 1,25(OH)D by expression of CYP27B1 in the microenvironment is now recognized as a paracrine pathway of immune regulation.¹²

Numerous in vitro studies have provided mechanistic explanations for the potential immunoprotective effects of vitamin D.¹³ Binding sites for the VDR have been identified in genes associated with CD, and vitamin D has been shown to enhance the production of interleukin-10 (IL-10) and induction of regulatory T cells.^{14–16} However, patients treated with vitamin D have also been noted to have increased IL-6 levels and an expansion of CD4⁺ T cells.¹⁷ Other studies on the effect of vitamin D on proliferation of T lymphocytes have produced conflicting results.^{18,19} Vitamin D also plays a role in the ability of human macrophages to kill intracellular bacteria, and dysfunction in this process has been associated with the risk of CD.^{20,21} There is recent evidence to support a protective role for vitamin D within epithelial cells against intestinal inflammation, independent of immune cells.²²

If low vitamin D levels are a consequence of inflammation, these should correlate with disease activity and be reversed by treatment of the underlying inflammation. Previous studies in patients have reported that low vitamin D levels were associated with lower quality of life and higher disease activity scores.^{6,23} Little is known about the effects of treatment of active CD with antitumor necrosis factors (anti-TNFs) on vitamin D pathways. We sought to measure vitamin D, VDR, and CYP27B1 levels in the peripheral blood of patients with CD, correlate with biomarkers, and to determine how these were affected by anti-TNF treatment.

MATERIALS AND METHODS

Patients

Patients were prospectively recruited from the Inflammatory Bowel Disease Center at Beth Israel Deaconess Medical Center, Boston. The study was approved by the institutional review board. Age, gender, duration of disease, current medications (including vitamin D supplements), and season of enrollment was recorded for each patient. Activity of disease at enrollment was determined by clinical scores (Harvey–Bradshaw Index [HBI]) and laboratory values (C-reactive protein [CRP]). An HBI score >5 was considered “active” disease.²⁴ A subset of the cohort was enrolled before commencement of infliximab loading and had HBI and vitamin D measured at enrollment, and 2 weeks later.

Blood Isolation

Each patient had 10 mL of heparinized whole blood and 5 mL of serum collected at enrollment, and the subset had a second sample collected 2 weeks later. Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient separation as previously described.¹⁷ CD4⁺ T cells were isolated using the RosetteSep Human CD4⁺ T-Cell Enrichment Cocktail (Stemcell Technologies, Vancouver, Canada). Serum and PBMCs were frozen at -80°C unless being used immediately.

Vitamin D Measurement

Serum vitamin D levels (25(OH)D) were measured by using a commercial solid phase enzyme-linked immunoassay kit (Calbiotech, San Diego, CA). Briefly, 10 µL of each sample was incubated in anti-vitamin D antibody-coated wells at room temperature for 90 minutes according to the manufacturer's instructions. This kit has been independently demonstrated to have a lower limit of quantification of 1.25 ng/mL and upper limit of 150 ng/mL.²⁵ The intra-assay variation is <6%, and total imprecision is <8%. The specificity for vitamin D3 is 100%. The manufacturers do not provide a reference range for New England.

Reverse Transcription Polymerase Chain Reaction

Messenger RNA (mRNA) was extracted from CD4⁺ T cells that were isolated from patients with CD using the Qiagen RNeasy Mini Kit (Qiagen, Valencia, CA). TaqMan VDR, CYP27B1, and CYP24A1 gene expression primers were obtained from Invitrogen (Grand Island, NY). Quantitative polymerase chain reaction was performed on the mRNA extracted from CD4⁺ T cells using the 7700 Sequence Detector (Applied Biosystems, Foster City, CA) and TaqMan technology as previously described.²⁶ The expression of 18S ribosomal subunit was used as the internal control. Data were analyzed using the relative standard curve method.

CD4⁺ T-cell Proliferation

About 2×10^5 CD4⁺ T cells were suspended in 96-well plates (Sigma-Aldrich, St. Louis, MO) with 200 µL of RPMI, 50 U/mL of IL-2, penicillin, and streptomycin. The CD4⁺ T cells were stimulated with 1.25 µL of anti-CD3/CD28 (Invitrogen). After 3 days of incubation, 10, 50, and 100 nM of 1,25 vitamin D3 (Sigma-Aldrich) was added to the wells. On the sixth day, 0.25 µCi of thymidine (Perkin Elmer, Waltham, MA) was added to each well. Proliferation was measured on day 7 through Beckman LS 6500 Scintillation Counter (Beckman Coulter Inc., Brea, CA).

Flow Cytometry

The same CD4⁺ T cells were stained with antibody-fluorochrome conjugates per manufacturer's methods at day 7 (eBioscience, San Diego, CA and BD Pharmingen, San Jose, CA). Fluorochromes include CD25 FITC and CD39 APC. The cells were incubated with FITC and APC conjugates for 30 minutes. FACSscan (Becton Dickinson, Franklin Lakes, NJ) was used for flow cytometry. Data were analyzed with WinMDI2.8 software.

Data Analysis

Mean and SD were recorded for continuous variables. For continuous variables, *t* test or analysis of variance was used to compare mean between individual or across groups. For categorical variables, χ^2 or Fisher's exact test was used where appropriate to compare frequencies. Spearman's *r* was generated to correlate nonparametric continuous variables with vitamin D levels. To account for seasonal variations in vitamin D in New England and small sample size, the year was dichotomized to a "high" season (June to November) and a "low" season (December to May). All data were analyzed using JMP software (version 8.0; SAS Institute, Cary, NC), and figures were generated using GraphPad Prism (version 5.0; GraphPad Software Inc., La Jolla, CA).

RESULTS

Thirty-seven patients were enrolled in the study, 20 with active disease and 17 in remission. Table 1 describes the patients' baseline characteristics. Serum vitamin D levels were not significantly different between seasons (June to November, mean 36 ng/mL; and December to May, 28 ng/mL) or according to reported supplement use (taking, mean 44 ng/mL; not taking, 33 ng/mL). However, mean serum vitamin D level at enrollment in patients with active disease was 27 ng/mL (± 2) compared with 38 ng/mL (± 3) in those in remission ($P = 0.02$ by *t* test) (Fig. 1). Serum vitamin D levels correlated with HBI scores (Spearman's $r = -0.5$, $P = 0.005$), but not with CRP levels (Fig. 2A, B).

In 8 patients, we measured vitamin D levels at the time of active inflammation (day 0) and at 14 days after receiving infliximab therapy (day 14). Mean serum vitamin D levels were 23 ng/mL (± 3) before anti-TNF and 40 (± 4) ng/mL 2 weeks later ($P < 0.005$ by paired *t* test). Seven of the 8 had higher serum vitamin D level after infliximab, and 5 of the 8 had a significant decline in the HBI scores (>3 decrease) after treatment (Fig. 3A, B). Mean CRP after infliximab (3.2 mg/L, SD = 2.4) was significantly lower than preinfliximab levels (mean 18.4 mg/L, SD = 18, $P = 0.04$ by Mann-Whitney test). We analyzed the change in serum vitamin D levels (delta) according to "clinical response" (HBI drop >3). The mean increase in serum vitamin D levels after infliximab was similar in both responders (mean 15 ng/mL, SD = 9) and nonresponders (mean 18 ng/mL, SD = 7), suggesting early improvements in vitamin D levels were independent of symptom scores. Only 1 of 8 patients reported taking vitamin D supplements during his infliximab treatment period.

Because circulating 25(OH) D requires the enzyme CYP27B1 to convert to active 1,25(OH)D and expression of the VDR for immunologic activity, we next measured expression of these genes in the CD4⁺ PBMCs of patients with CD. Mean gene expression (fold change) of VDR and CYP27B1 in PBMCs was higher in those with active CD when compared with those with inactive CD ($P = 0.057$ for VDR, $P < 0.001$ for CYP27B1, Fig. 4A, B). There was no correlation between serum vitamin D levels and VDR expression in these samples (data not shown).

Finally, we measured the immunological effects of raising vitamin D levels in patients with active CD. The stimulated polyclonal proliferation of CD4⁺ T cells increased from a baseline rate of 95,125 counts per minute (cpm) to 148,740 cpm (56% increase) with the

addition of 10 nM or 50 nM of vitamin D. This change was not statistically significantly (Fig. 5A). To determine if vitamin D was associated with induction of regulatory T cells (CD25⁺CD39⁺), we performed flow cytometry to measure the proportion of CD25⁺ and CD39⁺ T cells in the CD4⁺ pool. The proportion of CD25⁺ cells among the stimulated CD4⁺ population increased by 3-fold in the presence of vitamin D at 50 nM, but the proportion of CD39⁺ cells remained unchanged (Fig. 5B).

DISCUSSION

We demonstrate that vitamin D levels inversely correlate with disease activity in patients with CD. Consistent with the literature, we report that patients with active CD exhibit lower serum vitamin D levels than those in clinical remission. Jorgensen et al²⁷ reported serum vitamin D values in 182 patients with CD and noted an inverse relationship between vitamin D levels and CDAI scores, which was independent of smoking status or body mass index in a regression model. A Japanese cohort of 33 patients with CD also noted an association between CDAI scores, disease duration, and low vitamin D levels; these associations remained significant after multivariate analyses.²⁸ We add additional data to this literature by demonstrating early increases in serum vitamin D levels with clinical response to anti-TNF therapy. This effect may not be explained by improved absorption alone and would suggest that serum levels are responsive to the burden of systemic inflammation. Previous studies have reported improvements in nutritional status and metabolism after infliximab therapy but did not measure vitamin D levels per se.^{29,30}

As expected, VDR gene expression was higher in active disease in our patients, but this was not directly correlated with serum 25(OH)D levels. Previous studies have associated PBMC VDR expression with autoimmune diseases, albeit this was independent of serum vitamin D levels.^{31,32} IFN- γ and activation of T cells, both seen in patients with active CD, can induce upregulation of VDR in this setting.^{19,33,34} Similarly, TNF, IFN γ , and IL-1 can also induce CYP27B1 expression by monocytes in the inflammatory milieu.³⁵ The presence of these enzymes would readily permit the conversion of 25(OH)D to 1,25(OH)D and the activation of VDR to undertake local immunoregulatory effects.² Supportive of this, our finding shows that the CD4⁺ T-cell population expanded in the presence of elevated levels of vitamin D ex vivo, but these were predominantly CD25⁺ cells. CD4⁺CD25⁺ T cells exhibit suppressive functional properties on CD25⁻ cells, consistent with a regulatory phenotype. Previous studies have reported variable effects of vitamin D on T cells; vitamin D increased proliferation of CD4⁺CD25⁺ T cells and overall CD4⁺ T cells, but decreased numbers of CD4⁺ RO⁺/RA⁺ T cells.^{17,36,37} Further analyses would be required to characterize the functional activity of vitamin D-responsive cells in more depth.

Limitations of this study include the small sample size, which may lead to type 2 statistical errors and precludes multivariate regression model analysis. Most of our patients had only a single sample analyzed, and such observational associations do not prove causality. Further analysis of a larger cohort, pretreatment and posttreatment of their CD, would be required to validate these results. We did not objectively confirm active inflammation in patients with elevated HBI scores, although all patients with an HBI >5 had a CRP >3 mg/L. In addition,

confounders that could have led to increases in vitamin D levels aside from reduction in inflammation could not be accounted for.

In conclusion, our study provides evidence that serum vitamin D levels reflect disease activity in patients with CD, which can be altered by anti-TNF therapy. Patients with active CD exhibit lower vitamin D levels, counter-balanced by a compensatory increase in PBMC, VDR, and CYP27B1 to maximize vitamin D3 production. From a clinical viewpoint, low levels of vitamin D should not be interpreted in isolation, but in the context of the patient's disease activity at that time, and warrant repeated testing once in remission.

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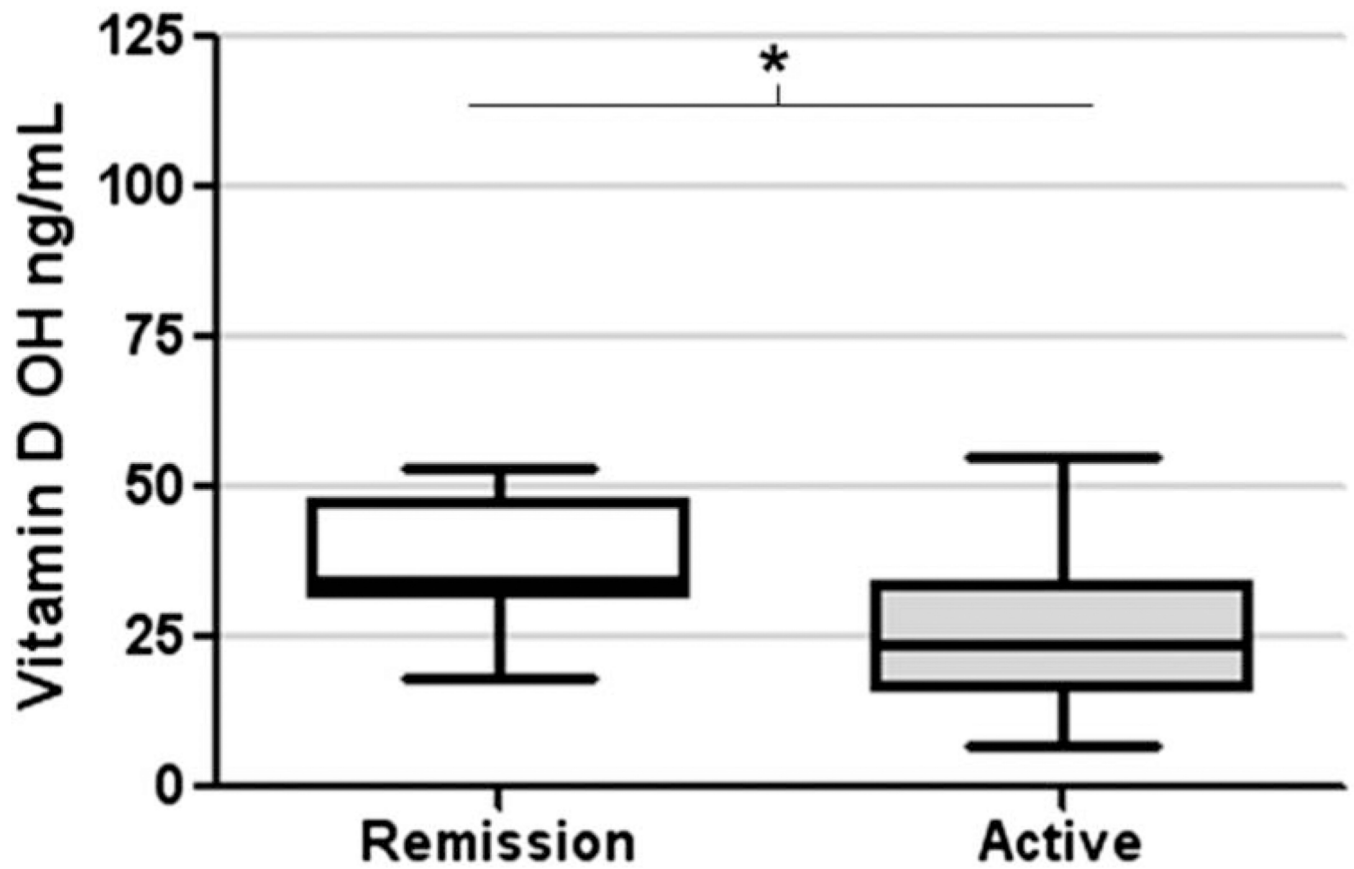


FIGURE 1. Mean serum vitamin D levels in patients in remission (white box) or with active CD (gray box) (* $P < 0.05$).

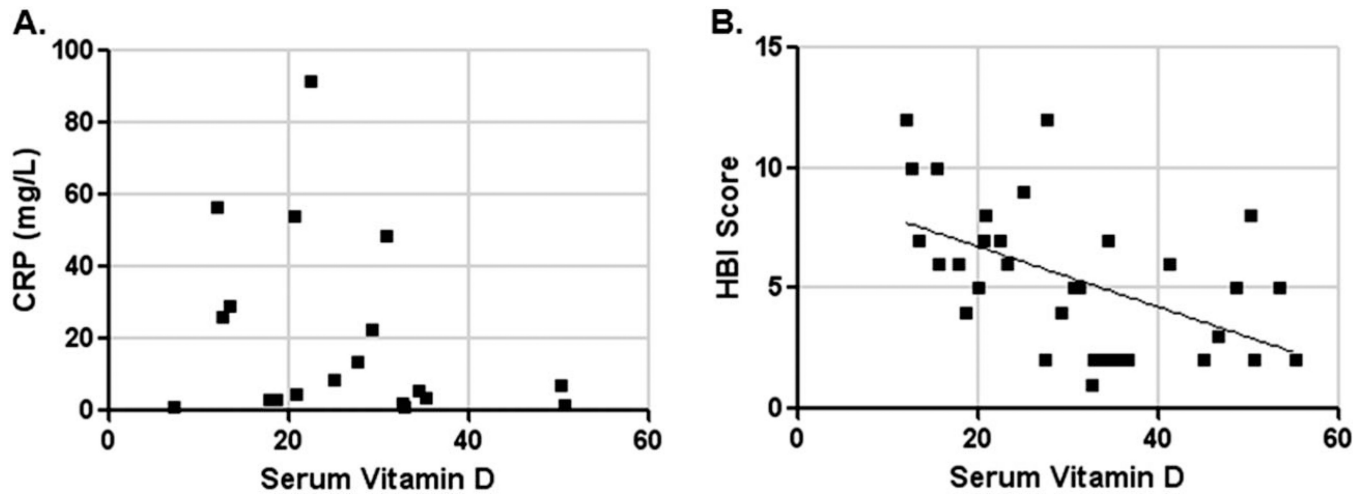


FIGURE 2. X–Y plot of serum vitamin D against CRP (A) and HBI score (B). Diagonal line represents logistic regression line ($P = 0.005$).

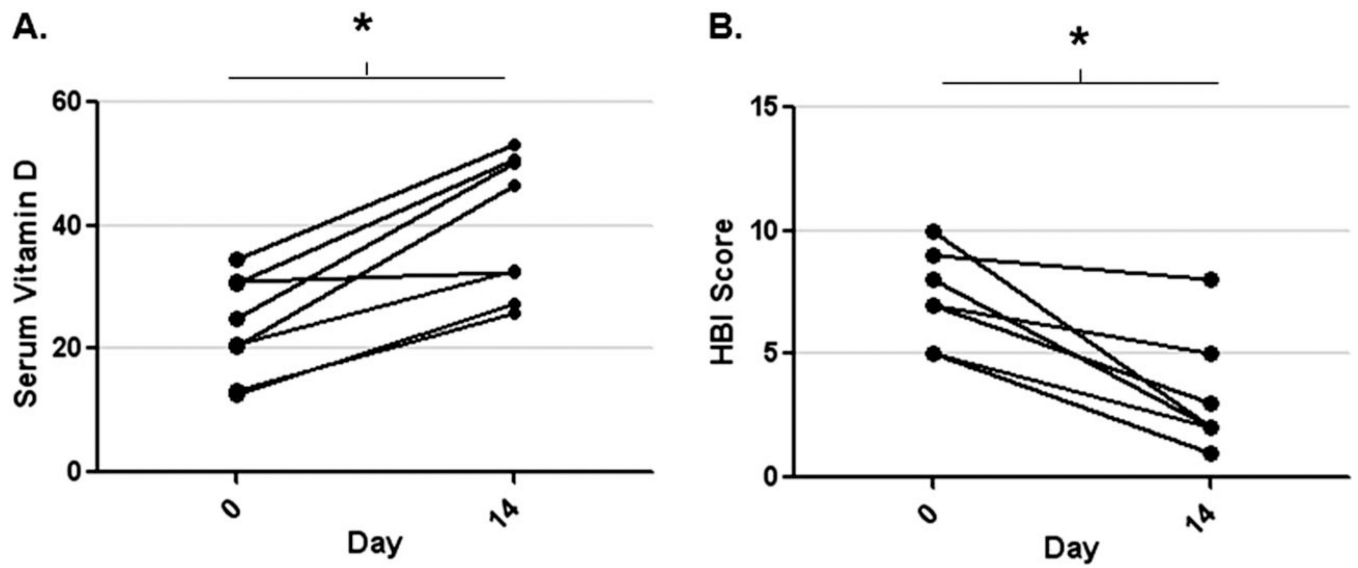


FIGURE 3. Paired serum vitamin D levels in patients on day 0 and day 14 after an infliximab infusion (A) and HBI scores in the same patients on day 0 and day 14 (B) ($*P < 0.05$).

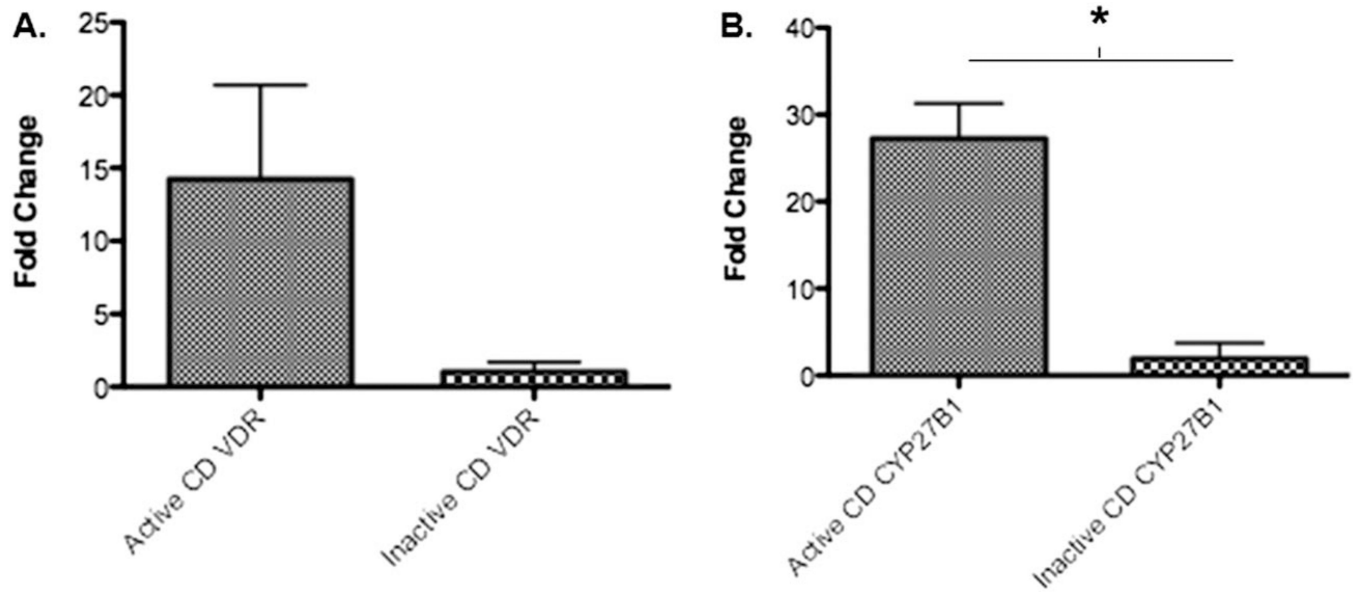


FIGURE 4.

Gene expression (fold change to normal) in CD4⁺ PBMCs of VDR gene (A) and CYP27B1 gene (B) in patients with CD.

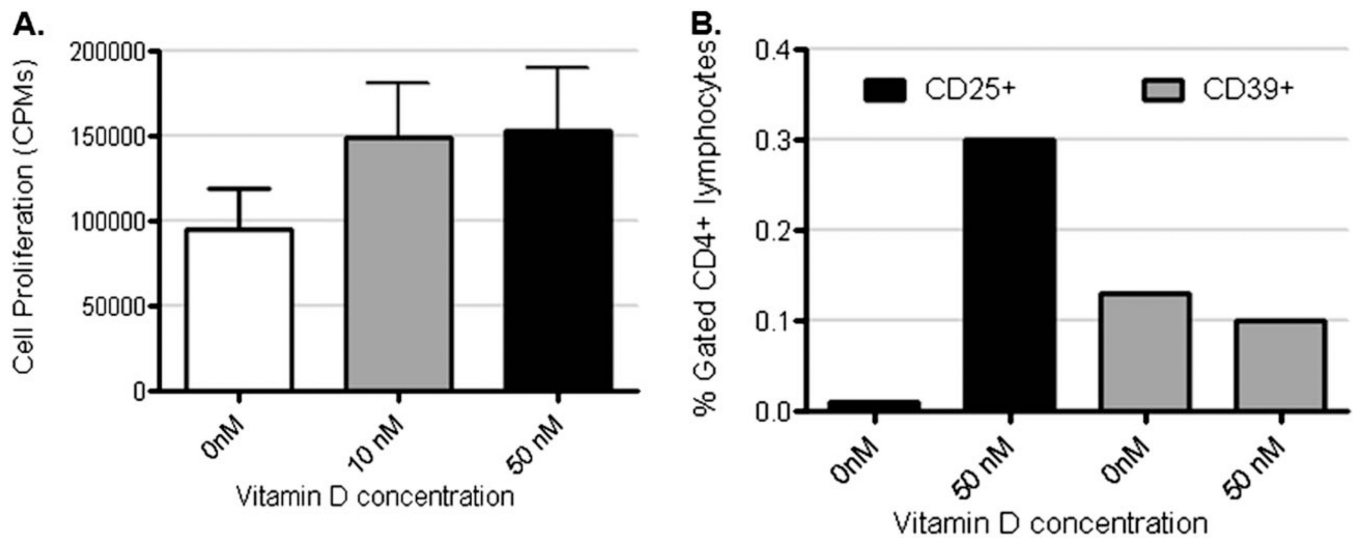


FIGURE 5.

A, Cell proliferation of CD4⁺ PBMCs in increasing concentrations (0, 10, 50 nM) of vitamin D in vitro. B, Proportion of CD4⁺ PBMCs that were CD25⁺ (black columns) or CD39⁺ (gray columns) after being cultured with different concentrations (0, 50 nM) of vitamin D ex vivo (x axis) for 3 days.

TABLE 1

Patient Characteristics (N = 37)

Variable	Active	Inactive
Mean age (STD), yr	34 (12)	30 (14)
Women, %	50	47
Smoker, %	10	6
Mean weight in lbs	162 (53)	147 (24)
Mean duration of disease (STD)	8 (11)	6 (12)
Disease behavior, %		
B1	30	65
B2	20	0
B3	35	24
Current medications, %		
Steroids	30	24
Mean HBI score (STD)	8 (2)	2 (1)
Mean CRP in mg/L (STD)	27 (26)	3 (2)

STD, standard deviation.