Randomized Trial of Vitamin D Supplementation to Prevent Seasonal Influenza and Upper Respiratory Infection in Patients With Inflammatory Bowel Disease

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Background: We evaluated whether oral vitamin D supplementation during the winter and early spring reduces the incidence of influenza and upper respiratory infections in patients with inflammatory bowel disease (IBD).

Methods: A randomized, double-blind, controlled trial was conducted to compare the effects of vitamin D supplementation (500 IU/day) and a placebo. The primary outcome was the incidence of influenza; the secondary outcome was the incidence of upper respiratory infection. Prespecified subgroup analyses were performed according to 25-hydroxyvitamin D (25-OHD) levels (low <20 ng/mL or high ≥20 ng/mL) and whether ulcerative colitis (UC) or Crohn's disease (CD) was present. We also used the Lichtiger clinical activity index for patients with UC and the Crohn's Disease Activity Index (CDAI) for patients with CD before and after interventions.

Results: We included 223 patients with IBD and randomized them into 2 groups: vitamin D supplementation (n = 108) and placebo (n = 115). The incidence of influenza did not differ between the groups. However, the incidence of upper respiratory infection was significantly lower in the vitamin D group (relative risk [RR], 0.59; 95% confidence interval (CI), 0.35–0.98; $P = 0.042$). This effect was enhanced in the low 25-OHD level subgroup (RR, 0.36; 95% CI, 0.14–0.90; $P = 0.02$). With respect to adverse events, the Lichtiger clinical activity index score was significantly worse in the vitamin D group ($P = 0.002$) and remained significant only in the high 25-OHD level subgroup.

Conclusions: Vitamin D supplementation may have a preventative effect against upper respiratory infection in patients with IBD but may worsen the symptoms of UC.

Key Words: vitamin D_3 supplementation, Crohn's disease, ulcerative colitis

INTRODUCTION

In recent years, vitamin D has been shown to have multifaceted effects on bone metabolism and has been shown to be associated with cardiovascular disease,[1, 2] renal disease,[3–5] and malignant tumors.[6, 7] Vitamin D deficiency is considered to reduce the adaptive and innate immune response and increase the risk of infection on the basis of in vitro and animal examinations.[8] Various cohort studies have also indicated that serum vitamin D deficiency increases the prevalence of infectious diseases.[9, 10] Previously, we demonstrated that vitamin D supplementation reduced the risk of influenza by 40%.[11] Moreover, it has been shown that vitamin D supplementation prevented 20% of acute respiratory infections in a meta-analysis of 25 randomized, placebo-controlled trials.[12]

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A meta-analysis indicated that patients with inflammatory bowel disease (IBD) had a 64% higher chance of vitamin D deficiency than non-IBD controls.[13] Vitamin D deficiency in IBD is considered to be caused by an absorption disorder due to bowel inflammation or small intestine resection, inadequate exposure to sunlight, inadequate intake of vitamin D, or adverse effects from therapeutic drugs.[14]

The risk of pneumonia in patients with IBD has been reported to be higher than that in patients without IBD. Patients with IBD, especially those taking medications such as corticosteroids and narcotics, are at increased risk of pneumonia.[15] The European Crohn's and Colitis Organization has indicated that influenza infection may be more severe in patients with IBD who take immunomodulators than among those not taking them.[16] The influenza vaccine is not considered to be as effective for patients with IBD as it is in the general population.[17]

In patients with IBD, there have been no previous reports of the prevention of influenza and upper respiratory infection using vitamin D supplementation. We therefore conducted a randomized, double-blind, placebo-controlled trial of vitamin D supplementation in patients with IBD to elucidate whether preventative intake of vitamin D supplements during the winter and early spring could reduce subsequent influenza and upper respiratory infections. The intention was to clarify whether these respiratory infections are caused by immunosuppressive treatment alone or if they are preventable by vitamin D supplementation.

MATERIALS AND METHODS

Study Design

We conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial at 4 hospitals in Japan over a 6-month period (from October 1, 2014, to March 31, 2015). The study protocol was reviewed and approved by the ethics committee of Jikei University School of Medicine (N0 25–2977432), and the trial was registered in the UMIN Clinical Trial Registry on August 1, 2014 (UMIN ID: 000014743). Both vitamin D and the placebo were purchased from Zenyaku Co. Ltd., Tokyo, Japan. The data monitoring center was the Division of Epidemiology at the Jikei University School of Medicine. None of the authors has a conflict of interest with the pharmaceutical company that made the vitamin D supplements.

Study Population, Eligibility, and Consent

Patients with ulcerative colitis (UC) or Crohn's disease (CD) diagnosed by a gastrointestinal specialist were recruited from August 2014 through October 2014 and followed-up at 1 of the 4 branch hospitals of Jikei University School of Medicine in Tokyo and Chiba, Japan. The following participants were eligible: those 18–80 years of age, those in a stable condition, and those with no contraindications to the study treatment. The exclusion criteria were as follows: 1) patients with a history of influenza virus infection from May 1, 2014, and beyond; 2) patients with a history of urinary stones; 3) patients who had taken vitamin D supplementation or active vitamin D medications; and 4) patients allergic to vitamin D supplements. All participants provided written informed consent.

Randomization, Blinding, and Intervention

One of the authors (AN) who did not see study participants generated a random allocation sequence (ie, study identification numbers) based on permutated blocks of 4 using a computerized procedure. Supplements and placebo were supplied in identical bottles containing capsules that appeared and tasted identical, and the allocation to either group was concealed by numbering. Because this blinding process was completed by staff and the author AN at Jikei University School of Medicine, both patients and medical staff at the 4 branch hospitals were completely unaware of the assignments throughout the trial period.

The vitamin D group was administered 500 IU per day. The supplements were prepacked in bottles and consecutively numbered for each patient according to the randomization schedule. The blinding process was performed by office secretaries who monitored and fixed the data, had no clinical involvement in the trial, and did not perform statistical analyses. The patients were assigned to groups, given the corresponding bottles, and asked to take 2 capsules per day for 6 months.

Follow-Up Procedure and Outcome Assessment

The primary outcome was influenza infection diagnosed using influenza virus test kits. We did not include influenza-like illnesses diagnosed without the use of kits. The secondary outcome was upper respiratory infection diagnosed by a clinician. A clinician evaluated the outcomes during the study period at each visit. In addition, we used a questionnaire to assess influenza infection and upper respiratory infection in all participants and included the following questions: "Have you had influenza vaccination?", "Have you had a fever over 37.5°C?"; "Have you had any symptoms in your upper respiratory tract?"; "Have you visited the hospital and received any treatment?"; "Have you received an influenza rapid test?"; and "If you received an influenza test, was the result positive or negative and was it influenza A or B?" In the present study, we included both viral and bacterial infections in the outcomes. Because the frequency of bacterial testing, rapid testing, and the prescription of antibiotics depend on each clinician's practice pattern, we did not choose these data as outcomes. Patients visited the hospital on a monthly basis and a clinician evaluated their clinical status, including disease activity and laboratory data. In addition, a clinician confirmed the events of influenza and upper respiratory infections. To evaluate the effect of vitamin D on disease activity, we used the Lichtiger clinical activity index for patients

with UC and the Crohn's Disease Activity Index (CDAI) for patients with CD before and after intervention.[18, 19] At the time of entry into the study and 2 months later, we measured the following laboratory parameters: peripheral blood calcium level, phosphorus level, C-reactive protein level, intact parathyroid hormone (iPTH) level, 25-OHD level, liver function, and renal function. The levels of 25-OHD and iPTH were analyzed at SRL Inc. (Hachioji, Tokyo, Japan). Serum levels of 25-OHD were measured by radioimmunoassay, as described previously, every year (within the same calendar month) after starting supplements.[20] Intact PTH was measured by electrochemiluminescence immunoassay.

Statistical Analysis

We estimated that the primary outcome would occur in 15% of the patients with IBD in the placebo group. The ability of vitamin D to protect against influenza infection was estimated at a 50% reduction in the outcome with a type I error (2-sided) of 5% and a power of 80% on the assumption of a 10% rate of loss to follow-up. We calculated that 244 participants were needed for the study. Efficacy was assessed using an intention-to-treat analysis. Continuous variables were compared using the Wilcoxon rank sum test and the Student *t* test, as appropriate. Categorical variables were assessed using the χ^2 test. The incidences of the primary and secondary outcomes were compared between the 2 groups using relative risks (RRs) and 95% confidence intervals (CIs). We also analyzed these outcomes after grouping the patients by disease (UC or CD) and 25-OHD levels (<20 ng/mL or ≥20 ng/mL). We tested the null hypothesis of the equality of risk ratios between the demographic groups using the χ^2 test. The changes in the serum 25-OHD, calcium, and iPTH levels after intervention were evaluated using paired *t* tests. In addition, the Lichtiger clinical activity index for patients with UC and the CDAI for patients with CD were analyzed using the Student *t* test and the Wilcoxon signed rank test, as appropriate. All reported *P* values were 2-sided, and those <0.05 were considered statistically significant. No adjustments were made for multiple comparisons. All analyses were performed using Stata 13.0 software (Stata Corp. LP, College Station, TX, USA).

RESULTS

Characteristics of the Study Population

A total of 237 patients were assessed for eligibility and enrolled into the study. Of these, 118 were randomly assigned to receive placebo, and 119 were randomly assigned to receive vitamin D (Fig. 1). In the placebo group, 10 participants withdrew from the study for the following reasons: 5 patients withdrew their consent, 1 patient had their participation terminated by the investigator, and 4 patients were lost to follow-up. In the vitamin D group, 4 patients withdrew from the study for the following reasons: 3 patients withdrew their consent, and 1 patient was lost to follow-up. The patient characteristics were not significantly different between the 2 groups (Table 1). The mean ± standard deviation of patient age was 44.7 ± 13.3 years. The distribution of diseases was as follows: 168 (75.3%) patients had UC, and 55 patients (24.7%) had CD. The mean 25-OHD level was 23.2 ± 8.3 ng/mL and the median iPTH concentration was 34 (range: 26–43) pg/mL. A low 25-OHD level (<20 ng/mL) was found in 77 patients (34.5%).

Change in Serum 25-OHD, Calcium, and iPTH Levels

Serum 25-OHD levels in the vitamin D group significantly increased ($P < 0.001$) (Fig. 2A), whereas the 25-OHD levels decreased in the placebo group ($P < 0.001$). Moreover, the serum iPTH concentration significantly decreased in the vitamin D group ($P = 0.015$) (Fig. 2B). In the placebo group, the serum iPTH concentration did not change significantly

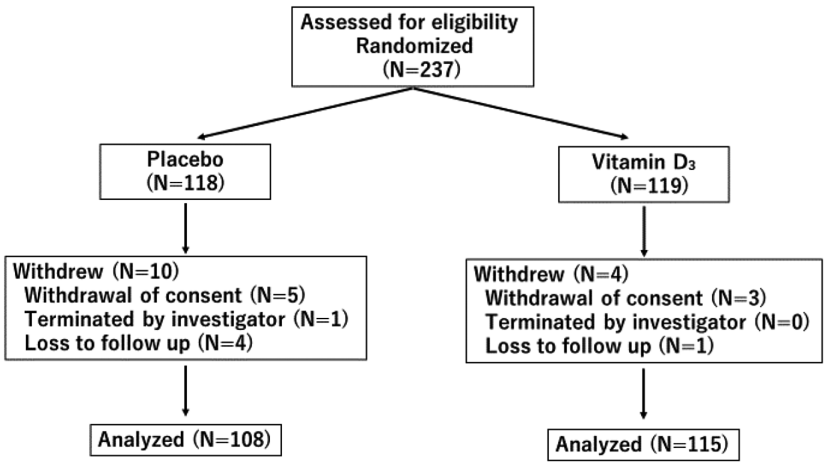

FIGURE 1. Patient flowchart.

TABLE 1. Clinical Characteristics of Patients With Inflammatory Bowel Disease

Characteristic	Placebo Group (n = 108)		Vitamin D_3 Group (n = 115)		*P*
Age (years)	45.4	± 1.4	44.1	± 1.2	0.482
Male (%)	66	(61.1)	70	(60.9)	0.971
Disease					
Ulcerative colitis (%)	80	(74.1)	88	(76.5)	0.642
Crohn disease (%)	28	(25.9)	27	(23.5)	0.216
Smoking					
Non-smoker (%)	79	(73.2)	89	(77.4)	0.552
Past smoker (%)	13	(12.0)	6	(5.2)	0.148
Current smoker (%)	16	(14.8)	20	(17.4)	0.564
Height (cm)	165	± 8	165	± 8	0.967
Body weight (kg)	60.2	± 10.2	61.2	± 11.5	0.496
Body mass index (kg/m^2)	22.0	± 2.9	22.4	± 3.4	0.405
Total protein (g/dL)	7.4	± 0.5	7.3	± 0.4	0.172
Albumin (g/dL)	4.3	± 0.4	4.3	± 0.3	0.368
Blood urea nitrogen (mg/dL)	12.4	± 2.7	12.5	± 3.3	0.938
Creatinine (mg/dL)	0.8	± 0.2	0.8	± 0.1	0.605
Sodium (mEq/L)	139	± 16	133	± 33	0.156
Potassium (mEq/L)	4.3	± 0.4	4.2	± 0.3	0.131
Calcium (mg/dL)	9.5	± 0.4	9.4	± 0.3	0.026
Phosphate (mg/dL)	3.4	± 0.5	3.4	± 0.5	0.556
25-hydroxyvitamin D (ng/mL)	23.9	± 10.2	23	± 7.3	0.457
Parathyroid hormone (pg/mL)	36	(27–47)	34	(26–41)	0.429
C-reactive protein (mg/dL)	0.04	(0.04–0.1)	0.04	(0.04–0.11)	0.896
White blood cell (/μL)	5900	± 1600	5900	± 1700	0.879
Neut (/μL)	3600	± 1200	3500	± 1300	0.629
Lymp (/μL)	1800	± 600	1800	± 600	0.794
Haemoglobin (g/dL)	14.4	± 1.2	14.1	± 1.5	0.140
5-Aminosalicylic acid (oral) (%)	99	(93.4)	108	(95.6)	0.478
5-Aminosalicylic acid (local) (%)	24	(22.6)	21	(18.6)	0.458
Elemental diet (%)	6	(5.7)	14	(12.4)	0.080
Steroid (oral) (%)	0	(0.0)	1	(0.9)	0.325
Steroid (local) (%)	4	(3.8)	7	(6.2)	0.386
Azathioprine (%)	16	(15.1)	19	(16.8)	0.728
Tacrolimus (%)	0	(0.0)	3	(2.7)	0.087
Anti-TNFα(iv) (%)	13	(13.3)	14	(12.4)	0.978
Anti-TNFα(sc) (%)	11	(10.4)	9	(8.0)	0.536

after 2 months (P = 0.087). The serum calcium concentration did not change during the study period in either the vitamin D or the placebo group (Fig. 2C).

Incidence of Influenza and Upper Respiratory Infection

The incidences of influenza and upper respiratory tract infections are shown in Table 2. Although there was no difference in the incidence of influenza between the 2 groups, upper respiratory tract infections were significantly less frequent in the vitamin D group (19 of 115, 16.5%) compared with the placebo group (30 of 108, 27.8%; RR, 0.59; 95% CI, 0.35–0.98; P = 0.042).

We also categorized the patients on the basis of vitamin D level (<20 ng/mL or ≥20 ng/mL) before supplementation (Table 3). In the subgroup of patients with a low vitamin D level (<20 ng/mL), the incidence of upper respiratory tract infection was significantly lower in the vitamin D group (5 of

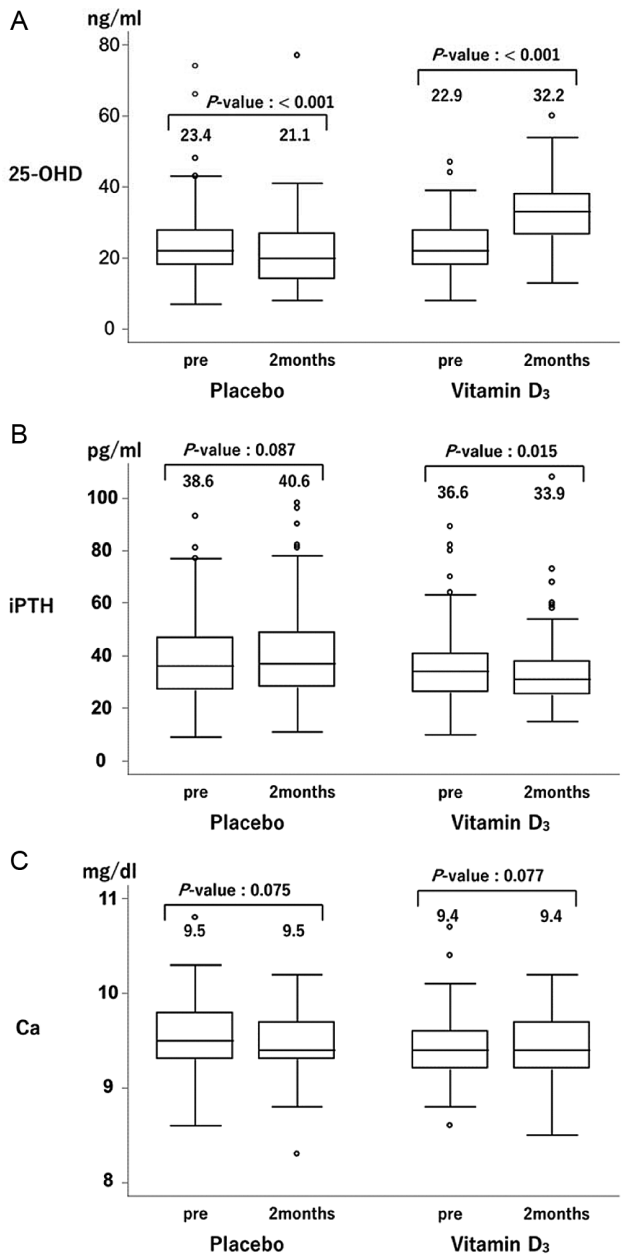

FIGURE 2. Change in 25-OHD, iPTH, and Ca after intervention.

40, 12.5%) than in the placebo group (13 of 37, 35.1%; RR, 0.36; 95% CI, 0.14–0.90; $P = 0.019$). In contrast, the incidence of upper respiratory tract infection was the same in the subgroup of patients with a higher vitamin D level (≥20 ng/mL) compared with the placebo group. The incidence of influenza was not different between the 2 groups for both low and high vitamin D level subgroups. We analyzed the influence of the use of steroids or immunosuppressive drugs (Table 4). There were no significant associations between vitamin D use and influenza infection both in steroid/immunosuppressive drug users and nonusers. Further, although the concentration of 25-OHD was not significantly different between steroid/immunosuppressive drug users and nonusers (23.0ng/mL vs 22.8 ng/mL), the vitamin D group showed a lower rate of upper respiratory infections among steroid/immunosuppressive drug nonusers (RR, 0.63; 95% CI, 0.38–0.98; $P = 0.047$).

Changes in Disease Severity Caused by Vitamin D

Patients with UC with remission rated below 3 points on the Lichitiger clinical activity index accounted for 75.3% of all patients. Patients with CD with remission rated below 150 on the CDAI accounted for 93.2% of all patients.

In patients with UC, the Lichtiger clinical activity index score did not change in the placebo group. However, in the vitamin D group, the score significantly increased after intervention (2.55 ± 0.21 to 3.24 ± 1.16; $P = 0.002$) (Table 5). These results were notably higher in the vitamin D subgroup (2.67 ± 0.27 to 3.40 ± 1.19; $P = 0.009$) but not in the vitamin D–insufficient subgroup. In patients with CD, the CDAI score did not significantly change before or after intervention in the placebo or vitamin D groups (Table 6). In addition, vitamin D status did not influence CDAI score.

Adverse Events

No patients developed serious adverse events, including urinary calculi and hypercalcemia, in either the placebo or the vitamin D groups.

DISCUSSION

In this randomized clinical trial, daily supplementation with 500 IU of vitamin D in patients with IBD between October and March showed a significant preventative effect against upper respiratory infections, although no significant difference was observed in the rates of influenza infection. There were fewer influenza infections during the study period compared with the previous year, and the influenza infection rate was 6.3% in patients with IBD in this study. Therefore, we were not able to prove the effectiveness of influenza prophylaxis using vitamin D supplementation in patients with IBD. Conversely, upper respiratory infections occurred in 22.0% of patients. A significant preventative effect was seen in the vitamin D–insufficient subgroup group (<20 ng/mL before supplementation), suggesting that maintaining 25-OHD levels at >20 ng/mL may be important to prevent upper respiratory infections. In subgroup analysis, the concentration of 25-OHD was not significantly different between steroid/immunosuppressive drug users and nonusers. Vitamin D supplementation reduced the upper respiratory infection rate in those IBD patients not on immunosuppressants but had no effect in immunosuppressed individuals. However, given wide confidence intervals for this finding, further confirmation in additional studies should be

TABLE 2. The Incidence of Influenza Virus Infection and Upper Respiratory Infection in the Vitamin D Group and Placebo Group

	Placebo	Vitamin D_3	Relative Risk	95% CI	*P*
No.	(n = 108)	(n = 115)			
Influenza infection	6 (5.6%)	8 (7.0%)	1.25	0.45–3.49	0.666
Upper respiratory infection	30 (27.8%)	19 (16.5%)	0.59	0.35–0.98	0.042

TABLE 3. The Incidence of Influenza Virus Infection and Upper Respiratory Infection by Vitamin D Status

25-OHD <20 ng/mL	Placebo	Vitamin D_3	Relative Risk	95% CI	*P*
No.	(n = 37)	(n = 40)			
Influenza infection	3 (8.1%)	2 (5.0%)	0.62	0.11–3.50	0.581
Upper respiratory infection	13 (35.1%)	5 (12.5%)	0.36	0.14–0.90	0.019
25-OHD ≥20 ng/mL	Placebo	Vitamin D_3	Relative risk	95% CI	*P*
No.	(n = 71)	(n = 75)			
Influenza infection	3 (4.2%)	6 (8.0%)	1.89	0.49–7.28	0.343
Upper respiratory infection	17 (23.9%)	14 (18.6%)	0.78	0.42–1.46	0.436

TABLE 4. The Incidence of Influenza Virus Infection and Upper Respiratory Infection According to the Use of Steroids or Immunosuppressive Drugs

No Steroid or Immunosuppressive Drug [a]Users	Placebo	Vitamin D_3	Relative Risk	95% CI	*P*
No.	n=76	n=76	—	—	—
Influenza infection	5 (6.6%)	6 (7.9%)	1.1	0.62–1.93	0.754
Upper respiratory infection	21 (27.6%)	11 (14.5%)	0.63	0.38–0.98	0.047
Steroid or Immunosuppressive Drug Users	Placebo	Vitamin D_3	Relative risk	95% CI	*P*
No.	n=32	n=39	—	—	—
Influenza infection	1 (3.1%)	2 (5.1%)	1.23	0.53–2.81	0.676
Upper respiratory infection	9 (28.1%)	8 (20.5%)	0.82	0.47–1.43	0.456

[a]Immunosuppressive drug: azathioprine, tacrolimus, anti-TNFα.

considered. No significant differences were observed in other subgroup analyses according to patient characteristics.

In patients with IBD, vitamin D level is inversely correlated with mucosal inflammation and disease activity.[21, 22] Another report indicated that patients with IBD and low mean vitamin D levels had worse disease severity, increased pain, increased need for additional therapies, and increased health care utilization.[23] In this study, low vitamin D levels (25-OHD <20 ng/mL) were seen in 34.5% of patients in the entire study population, in 33.3% of patients with UC, and in 38.1% of patients with CD. The concentration of 25-OHD did not show a significant correlation with disease activity. Reductions in 25-OHD have been reported to increase the rates of upper respiratory infections, and vitamin D supplementation could decrease the risk of infection.[12] Patients with IBD are thought to be at a higher risk of upper respiratory infections because of the use of corticosteroids, immunomodulators, and biological agents. Furthermore, it is thought that vitamin D insufficiency may increase the risk of infection. In this study, we were able to reduce the risk of upper respiratory infections in patients with IBD by elevating serum 25-OHD levels through vitamin D supplementation. In vitro examinations have shown that the role of vitamin D is to adjust innate immunity and regulate the adaptive effects on

TABLE 5. The Lichtiger Clinical Activity Index Score Pre- and Post-Intervention

	Lichtiger Clinical Activity Index				
	Pre-intervention		Post-intervention		*P*
Placebo	2.49	± 0.19	2.75	± 1.18	0.322
n = 80	—	—	—	—	—
Vitamin D_3	2.55	± 0.21	3.24	± 0.16	0.002
n = 88					
25-OHD < 20 ng/mL					
Placebo	2.63	± 0.37	2.85	± 0.32	0.577
n = 28					
Vitamin D_3	2.28	± 0.31	2.93	± 0.29	0.119
n = 28					
25-OHD ≥ 20 ng/mL					
Placebo	2.40	± 0.22	2.62	± 0.22	0.409
n = 52					
Vitamin D_3	2.67	± 0.27	3.40	± 0.19	0.009
n = 60					

TABLE 6. CDAI Score Pre- and Post-Intervention

	CDAI				
	Pre-intervention		Post-intervention		*P*
Placebo	68.1	± 43.9	65.3	± 44.6	0.178
n = 28					
Vitamin D_3	97.9	± 77.7	78.8	± 65.3	0.112
n = 27					
25-OHD < 20 ng/mL					
Placebo	89.1	± 21.2	65.1	± 17.0	0.213
n = 9	—	—	—	—	—
Vitamin D_3	100.3	± 29.3	88.7	± 28.9	0.232
n = 12	—	—	—	—	—
25-OHD ≥20 ng/mL	—	—	—	—	—
Placebo	61.5	± 9.10	100.3	± 29.3	0.568
n = 19					
Vitamin D_3	96.0	± 21.9	76.6	± 10.8	0.255
n = 15					

mucosal immunity after bacterial infections of the respiratory tract.[24] Furthermore, an immunomodulatory effect of vitamin D metabolites has been reported in the respiratory epithelial cells related to viral infection.[25]

In this study, the serum level of 25-OHD was increased using 500 IU vitamin D supplements. In our previous study,[11] supplementation with vitamin D at 1200 IU/day was preventive during the early phase but not during the later phase. We hypothesized that 25-OHD levels should be maintained at a level that is neither too low nor too high (eg, between 20 ng/mL and 40 ng/mL) to prevent influenza efficiently. However, our previous study did not measure serum levels of 25-OHD. The previous report showed that a daily intake of vitamin D in the range of 700 to 800 IU seems to be required to prevent winter seasonal increases in iPTH level and maintain stable bone turnover in young, healthy white men.[26] Many studies showed a preventive effect for infection with ≥1000 IU of vitamin D. However, another paper showed that additional supplementation with 400 IU/day of vitamin D prevented acute respiratory tract infections.[27, 28]

In fact, even with low doses of vitamin D, 25-OHD levels increased from 22.9 ng/mL to 32.2 ng/mL, with a significant decrease in iPTH level.

The increased levels of 25-OHD did not seem to affect serum levels of iPTH or calcium. With respect to IBD activity, the clinical activity score in patients with UC increased significantly in the vitamin D supplementation group. However, this was a minimal increase, and therefore, a change in the treatment of UC was not required. This change was not found in patients with CD. In this study, the number of patients with CD was too small to detect the effects of vitamin D on CDAI. Although the results of this study showed that vitamin D supplementation did not influence disease activity during the study period, future studies including sufficient numbers of patients with CD are needed to validate these findings. We recommend that clinicians check the patient's serum 25-OHD concentration before administering vitamin D to patients with IBD. If the serum 25-OHD level is sufficient, clinicians should be cautious of any negative effect of supplementation on symptoms. Further studies will be necessary to evaluate the influence of vitamin D supplements on patients with UC without vitamin D deficiency.

The major limitations of this study were the small sample size, the low number of influenza infections during the study period, that upper respiratory tract infection information was obtained via patient questionnaires, and that disease activity was relatively mild.

In conclusion, the results of the present study suggest that vitamin D supplementation during the winter and early spring may reduce the incidence of upper respiratory infection in IBD patients. This effect was prominent in patients with IBD who had low serum vitamin D levels before supplementation (<20 ng/mL).

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