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ORIGINAL ARTICLE

Impact of High-Dose Vitamin D3 Supplementation in Patients with Crohn's Disease in Remission: A Pilot Randomized Double-Blind Controlled Study

Neeraj Narula[1] · Mohan Cooray[1] · Rebecca Anglin[1] · Zack Muqtadir[1] · Alisha Narula[1] · John K. Marshall[1]

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Abstract
Aim To assess the tolerability and efficacy of high-dose vitamin D3 in patients with Crohn's disease (CD).
Methods This was a randomized, double-blind placebo-controlled trial of high-dose vitamin D3 at 10,000 IU daily ($n = 18$) compared to 1000 IU daily ($n = 16$) for 12 months in patients with CD in remission. The primary outcome was change in serum 25-hydroxy-vitamin D levels. Secondary outcomes included clinical relapse rates and changes in mood scores.
Results High-dose vitamin D3 at 10,000 IU daily significantly improved 25-hydroxy-vitamin D levels from a mean of 73.5 nmol/L [standard deviation (SD) 11.7 nmol/L] to 160.8 nmol/L (SD 43.2 nmol/L) ($p = 0.02$). On an intention-to-treat basis, the rate of relapse was not significantly different between patients receiving low- and high-dose vitamin D3 (68.8 vs 33.3%, $p = 0.0844$). In per-protocol analysis, clinical relapse of Crohn's disease was less frequently observed in patients receiving a high dose (0/12 or 0%) compared to those receiving a low dose of 1000 IU daily (3/8 or 37.5%) ($p = 0.049$). Improvement in anxiety and depression scores and a good safety profile were observed in both groups treated with vitamin D3.
Conclusions Oral supplementation with high-dose vitamin D3 at 10,000 IU daily significantly improved serum 25-hydroxy-vitamin D levels. Rates of clinical relapse were similar between both groups. Larger studies using high-dose vitamin D3 for treatment of inflammatory bowel diseases are warranted.
Clinicaltrials.gov registration no NCT02615288.

Keywords Crohn's disease · Ulcerative colitis · Inflammatory bowel disease · Vitamin D

Introduction

Vitamin D has been proposed to play a role in a variety of chronic inflammatory disorders, including Crohn's disease (CD). Vitamin D deficiency has been implicated in the development of CD, and its analogues may have a role in the treatment of CD [1, 2]. Current research also suggests a role for vitamin D in counteracting some IBD-specific complications, including osteopenia [3], colorectal neoplasia [4], and depression [5]. There remains a need for well-designed prospective studies to further delineate these relationships.

Vitamin D supplementation has been shown to reduce relapse rates of some immune-mediated disorders [6, 7]. Jørgensen et al. [2] randomized 108 patients with CD in remission to calcium 1200 mg daily and either 1200 IU of vitamin D3 or placebo daily for 12 months. A nonsignificant trend toward lower relapse rate was observed in patients treated with vitamin D3 (6/46 (13%) vs. 14/48 (29%), $p = 0.056$) [2]. The authors speculated that benefits may be more apparent if the dose of vitamin D3 used was higher. A recent observational cohort study showed doses of 10,000 IU daily to be safe in patients with Crohn's disease and associated with an improvement in symptoms [8].

In patients with Crohn's disease in remission, we hypothesized higher doses of vitamin D would more

✉ Neeraj Narula
Neeraj.narula@medportal.ca

[1] Division of Gastroenterology, Department of Medicine, Farncombe Family Digestive Health Research Institute, McMaster University, 1280 Main Street West, Unit 3V28, Hamilton, ON L8S 4K1, Canada

effectively improve 25-hydroxy-vitamin D levels and would be tolerated well without side effects of hypercalcemia. We also wanted to explore whether higher doses could reduce the clinical relapse rate of patients with Crohn's disease in remission, and if higher doses of vitamin D3 could improve depression and anxiety symptoms. In order to determine the safety and feasibility of using high-dose vitamin D3, we designed a pilot randomized double-blind controlled trial comparing doses of oral vitamin D3 at 10,000 IU daily to 1000 IU daily.

Methods

Study Design and Location

This was a single-center study carried out at McMaster University Medical Centre in Hamilton, Ontario, Canada. The inclusion period was from January 2014 to March 2015. The study was approved by the Hamilton Integrated Research Ethics Board (project 13-038), and informed consent was obtained from all recruited patients. The study was supported by a resident research grant provided by the Canadian Association of Gastroenterology in 2013.

Intervention

Patients were randomized to receive high-dose (10,000 IU) or low-dose (1000 IU) daily 25-hydroxy-vitamin D3 supplementation. The daily dose consisted of ten tablets for patients in both arms. Patients allocated to the high-dose group consumed ten 1000 IU tablets daily. Patients in the low-dose group consumed one 1000 IU tablet and nine identical placebo tablets daily. The dose of 10,000 IU daily was chosen based on prior evidence that this dose may be safe for patients with Crohn's disease [8]. Patient compliance was assessed by patient interview and measuring the weight of pills in the bottles. Based on the residual weight of the pill bottles at follow-up, the percentage of pills consumed could be estimated.

Inclusion Criteria

Adult patients aged 18–70 with a prior diagnosis of CD in clinical remission for at least 28 days with a Harvey–Bradshaw index (HBI) less than or equal to 4 were eligible to participate. All maintenance therapies for CD were required to be at a stable dose for at least 3 months before randomization, with no systemic steroid therapy in the preceding 4 weeks. Patients using vitamin D supplements at the time of enrollment were instructed to discontinue them for a period of at least 6 weeks before randomization, consistent with washout periods used in other studies [9, 10]. Exclusion criteria included pregnant women or women considering pregnancy during the study period, short-gut syndrome, and any condition which could predispose to vitamin D toxicity, including renal insufficiency (creatinine clearance less than 60 ml/min), sarcoidosis, hyperparathyroidism, or malignancy. Concomitant therapy with thiazide diuretics, barbiturates, digitalis, or supplemental products containing vitamin D was not permitted.

Randomization and Blinding

Vitamin D3 and placebo tablets were manufactured by Jamieson Laboratories (Windsor, Canada). Randomization of tablet bottles was conducted by Jamieson Laboratories prior to any patients being enrolled in the study, and tablets were provided to the study investigators at the study outset in prepackaged bottles labeled by subject number. Jamieson Laboratories maintained the list of randomization until the end of the study, and the study investigators did not have access to this list for the duration of the study. Jamieson Laboratories did not have any input into the study design or conduct, nor did they have any access to patient data. Patients who were recruited and consented to participate in the study were assigned identification numbers in sequential order that corresponded to study numbers on the tablet bottles. Each patient was given two containers. The first container had 365 tablets of vitamin D3 at a dose of 1000 IU per pill. All patients were instructed to consume one tablet daily from this container. The second container held 3285 pills, which were either 1000 IU tablets of vitamin D3 or identical placebo. Patients were asked to consume nine tablets from these containers daily. The study was performed using this method due to vitamin D capsules only being available at a dose of 1000 IU from the manufacturer. Patients and study investigators were blinded until the completion of the study.

Data Collection and Follow-Up

The duration of the intervention was one year. All maintenance therapies for CD that were being used prior to entering the trial were continued. Patients had scheduled follow-up at 3, 6, 9, and 12 months. Patients had blood tests performed at the beginning and end of the study, including complete blood count, C-reactive protein (CRP), calcium, albumin, and 25-hydroxy-vitamin D3 level. The Hamilton Regional Laboratory Medicine Program uses the automated DiaSorin Liaison 25-OH-vitamin D assay. Adverse events, changes in CD management including additional medications or surgeries, concomitant medications, and compliance were assessed at each follow-up. Any patient with symptoms of relapse or a potential adverse event in between follow-up visits was brought to

clinic for assessment, including the HBI score and laboratory assessment (including calcium levels). At the final visit, the HBI and Hospital Anxiety and Depression Scale (HADS) scoring tools were administered, in addition to the previously mentioned items of interest. Subjects were assessed every three months by a study investigator, usually in conjunction with the study coordinator.

Endpoints

The primary outcome of interest was the mean change in 25-hydroxy-vitamin D levels in each arm after 12 months. Secondary outcomes included the proportions of subjects who experienced adverse events including hypercalcemia (>2.55 mmol/L according to the Hamilton Regional Laboratory Medicine Program), relapse rates (defined as HBI score of 5 or more with an increase of ≥3 points from baseline, or initiation or escalation of existing or new therapies for Crohn's disease), CRP change after 12 months, and changes in mood (as assessed by HADS). A HADS score of greater than 10 was consistent with active depression and/or anxiety. A HADS score of 7 or less was consistent with a normal mood score. A HADS score reduction of 2 or more was considered to be clinically significant, as suggested in other studies [11]. Patients were assessed by a physician blinded to clinical data and treatment allocation.

Sample Size and Statistical Analysis

It has been demonstrated in a prior study that additional intake of 100 IU/day can improve 25-OH-vitamin D3 levels by approximately 0.4–0.8 ng/mL [12]. Using 0.4 ng/mL as a conservative estimate, it was estimated that the difference in mean 25-hydroxy-vitamin D levels between the 10,000 IU daily group and the 1000 IU daily group would be 36 ng/mL (or 90 nmol/L). Using an alpha level of 0.05, power level of 0.80, and a standard deviation of 90 nmol/L, it was determined a size of 16 patients per intervention arm would be needed to demonstrate significant improvement in the arm receiving high-dose therapy. Assuming 20% dropout, we planned to enroll a total of 40 patients.

Analyses were performed on an intention-to-treat basis and per protocol. Subjects lost to follow-up were assumed to have relapsed. Patients included in per-protocol analysis were those who completed the trial with at least 65% compliance Frequencies were compared using Fisher's exact test due to a low number of events. Continuous variables such as CRP and 25-OH-vitamin D3 levels were compared using Student's *t* test. Analyses were performed with GraphPad Prism (version 5.03; GraphPad Software, San Diego, CA).

Results

Patient Characteristics

We consented a total of 39 patients for inclusion in the study. After enrollment was complete, study drug was distributed to all patients over one week to allow simultaneous start of the intervention by all participants. Five participants who initially enrolled did not pick up their study drug and were excluded from analysis (Fig. 1). A total of 34 patients were randomly assigned to receive the high dose (10,000 IU daily) or low dose (1000 IU daily) of vitamin D3 daily. The baseline characteristics of patients assigned to each group were similar (Table 1). Rates of premature subject withdrawal were high. Among 16 patients in the low-dose arm, 8 withdrew, with reasons including side effects [1], a new diagnosis of breast cancer [1], possible sarcoidosis [1], relocation out of the country [1], or lost to contact [4]. The patient diagnosed with breast cancer was found to have a lump only one month into the study and underwent biopsy. She withdrew from the study after two months due to her diagnosis and anxiety about her upcoming surgery. Out of the 18 patients assigned to high-dose therapy, 6 patients withdrew for reasons including

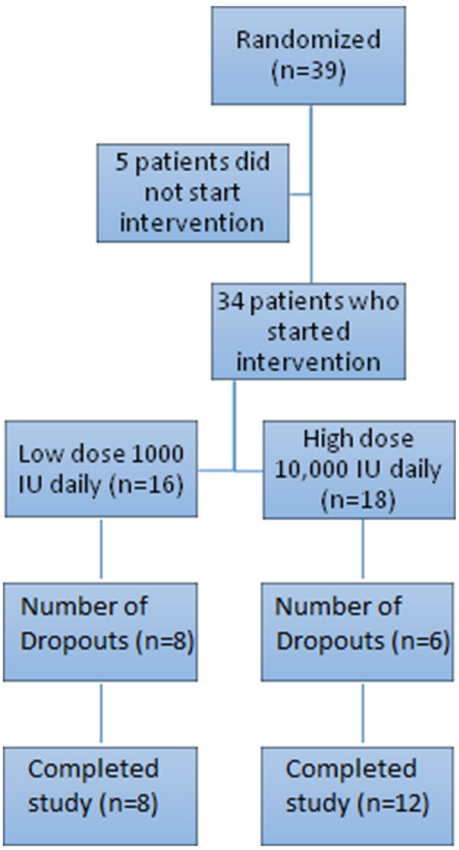

Fig. 1 Study flow diagram

Table 1 Baseline characteristics

	Low-dose vitamin D ($n = 16$)	High-dose vitamin D ($n = 18$)	P value
Female patients [n (%)]	10 (63)	10 (56)	0.74
Age (years), mean (s.d.)	35 (3)	33 (3)	0.62
Smokers [n (%)]	0 (0)	1 (5)	1
Patients with indoor occupation [n (%)]	16 (100)	18 (100)	
Disease site [n (%)]			
Ileum only	6 (38)	5 (28)	0.72
Ileum and colon	1 (6)	5 (28)	0.18
Colon only	9 (56)	8 (44)	0.73
Prior surgery for Crohn's disease [n (%)]	3 (19)	5 (28)	0.69
Medications (current)			
AZA/6-MP/MTX	6 (38)	8 (44)	0.74
Anti-TNF	5 (31)	11 (61)	0.10
Use of vitamin D at baseline	7 (44)	8 (44)	1
Baseline 25-OH-vitamin D level in nmol/L, mean (SD)	71.3 (7.3)	73.5 (11.7)	0.89

SD standard deviation

side effects [1], substantial traveling [1], or lost to follow-up [4]. A total of 8 patients from the low-dose arm and 12 patients receiving high-dose therapy completed the intervention.

Adverse Effects and Adherence to Therapy

Table 2 provides details on the adverse events experienced by patients completing the study. From the low-dose group, one subject complained of nausea and another experienced heartburn. From the high-dose group, one patient complained of excessive acne. Among patients who withdrew from the study due to side effects, one experienced excessive fatigue and another experienced headache. All patients who experienced side effects had calcium levels measured in the normal range. No reported adverse events were believed by the investigators to be directly attributable to vitamin D3 intake.

Among patients who completed the study, compliance was 65–80% for two patients in the high-dose arm and for one patient in the low-dose arm. The remainder of patients who completed the study were estimated to have 80% or greater compliance.

Effect of Vitamin D3 on Serum 25-OH-Vitamin D Levels

Baseline levels of serum 25-hydroxy-vitamin D were similar between the low- and high-dose vitamin D3 study arms [mean 71.3 nmol/L (SD 7.3 nmol/L) vs. mean 73.5 nmol/L (standard deviation (SD) 11.7 nmol/L), $p = 0.89$, Student's t test)]. Prior vitamin D3 use was reported among 44% of patients in both arms at dosing ranging from 400 to 1000 IU daily.

In the low-dose arm, mean serum 25-hydroxy-vitamin D levels did not change significantly, from 71.3 nmol/L (SD 7.3 nmol/L) at baseline to 82.8 nmol/L (SD 26.3 nmol/L) after 12 months ($p = 0.63$) (Fig. 2). In contrast, mean serum 25-hydroxy-vitamin D levels increased significantly

Table 2 Safety and tolerability of both doses of vitamin D3

	Low-dose vitamin D ($n = 8$)	High-dose vitamin D ($n = 12$)
Major adverse events		
Hypercalcemia	0	0
Hospitalization	0	0
Mortality	0	0
Minor adverse events		
Nausea	1	0
Heartburn	1	0
Acne	0	1

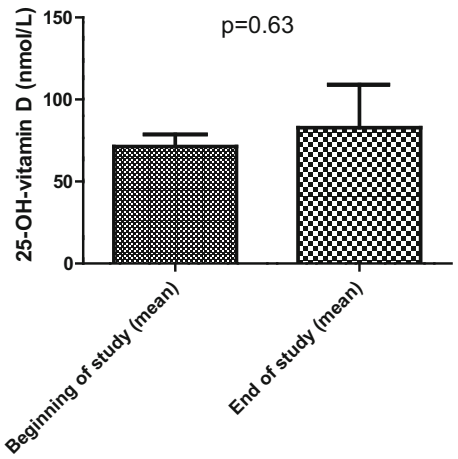

Fig. 2 Impact of low-dose vitamin D3 on mean serum 25-hydroxy-vitamin D level

in the high-dose arm from 73.5 (SD 11.7 nmol/L) to 160.8 nmol/L (SD 43.2 nmol/L) ($p = 0.02$) (Fig. 3).

Effect of Vitamin D3 on Maintenance of Remission

The impact of vitamin D3 on clinical symptoms is detailed in Table 3. On an intention-to-treat basis, if patients who withdrew from the study were assumed to have clinical relapse, no significant difference was seen in the rate of relapse, which was 68.8% (11/16 patients) in the low-dose group compared to 33.3% (6/18 patients) receiving high-dose therapy ($p = 0.0844$). On a per-protocol basis, 3 out of 8 (37.5%) patients in the low-dose vitamin D3 group experienced a clinical relapse, compared to 0 out of 12 (0%) patients receiving high-dose therapy ($p = 0.0491$). All three patients who experienced clinical relapse in the low-dose group required change in Crohn's disease management, including use of corticosteroids in all of them, and initiation of TNF-alpha antagonists in two of them. These three patients had investigations performed by their treating gastroenterologists that revealed objective findings of active inflammation (either through endoscopy or cross-sectional imaging) prior to escalation of therapy. No other patients in the low-dose group had change in their therapies for Crohn's disease. No patients from the high-dose group required escalation of therapy. One patient in the high-dose group who was using combination therapy with a TNF-alpha antagonist and methotrexate had a change in mode of administration of methotrexate from subcutaneous to oral at a similar dose. This was mainly due to convenience and not for change in symptoms, so this patient was not deemed as clinical relapse.

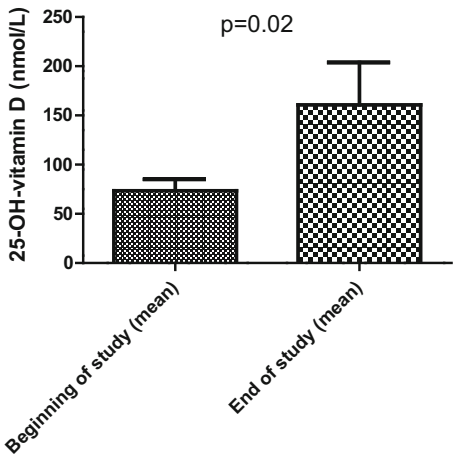

Fig. 3 Impact of high-dose vitamin D3 on mean serum 25-hydroxy-vitamin D level

Effect of Vitamin D3 on Serum CRP

After the 12-month period, the CRP values in the low- and high-dose group were similar ($p = 0.30$). Baseline levels of serum CRP were similar between patients who received low- and high-dose vitamin D3 [median 1.9 mg/L (interquartile range (IQR) 0.5–5.2 mg/L) vs. median 1.8 mg/L (IQR 0.6–19.9 mg/L) ($p = 0.48$)]. Oral vitamin D3 treatment with 1000 IU daily led to a reduction in CRP levels after 12 months, with a median CRP of 0.5 mg/L (IQR 0.5–0.7 mg/L), but this was not statistically significant ($p = 0.46$). Patients who were treated with 10,000 IU daily also had a reduction in CRP levels, with a decrease from a median of 1.8 mg/L (IQR 0.6–19.9 mg/L) to 1.5 (IQR 0.5–11.2 mg/L), but again this change was not significant ($p = 0.37$).

Effect of Vitamin D3 on Mood

As shown in Table 4, improvements in mood scores were seen in both low- and high-dose arms. Clinically significant reductions in HADS scores were seen in 9 of 11 (82%) patients receiving high-dose vitamin D and 4 of 7 (57%) patients receiving low-dose vitamin D. The improvement in HADS score did not differ significantly between both groups ($p = 0.33$). Among subjects with baseline HADS scores consistent with clinical depression and/or anxiety, mood scores normalized in 4 out of 7 (57%) subjects on high-dose therapy and 1 out of 4 (25%) subjects on low-dose therapy ($p = 0.55$). A sensitivity analysis was performed using an alternative HADS score threshold of 8 to define clinical depression and/or anxiety with similar results.

Discussion

This pilot study found that high-dose vitamin D3 at 10,000 IU daily significantly improved 25-hydroxy-vitamin D levels. No significant difference was observed in

Table 3 Relapse rates in patients consuming low- and high-dose vitamin D3

	Low-dose vitamin D ($n = 16$)	High-dose vitamin D ($n = 18$)	*P* value
Number of withdrawals			
Lost to follow-up	4	4	
Side effects	1	1	
Other	3	1	
Number of patients completing study	8	12	
Number of relapses (intention to treat—assumes all withdrawals relapsed)	11	6	
Relapse rate (per intention to treat) (%)	68.8%	33.3%	0.0844
Number of relapses (actual)	3	0	
Relapse rate (per protocol) (%)	37.5%	0%	0.0491

Table 4 Impact of vitamin D3 treatment on depression and anxiety

	Low-dose vitamin D	High-dose vitamin D	*P* value
Number of patients who completed HADS	7	11	
Number of patients with clinically significant reduction in HADS score [*n* (%)]	4 (57%)	9 (82%)	0.326
Number of patients with clinical depression/anxiety at baseline	4	7	
Number of patients who went from clinical depression/anxiety to normal mood [*n* (%)]	1 (25%)	4 (57.1%)	0.5455
Number of patients with clinically significant reduction in HADS score from baseline [*n* (%)]	2 (50%)	6 (85.7%)	0.4909

relapse rates between patients receiving high- and low-dose therapy ($p = 0.0844$). Both regimes appeared safe and well tolerated. The US National Institute of Health suggests doses of up to 4000 IU daily are safe, noting concern for vitamin D toxicity at doses between 10,000 and 40,000 IU daily, or at serum levels of 25-hydroxy-vitamin D between 200 and 240 ng/mL [13]. No toxicity was observed in this study in patients consuming 10,000 IU daily, and the highest level of 25-OH-vitamin D measured in this study was 325 ng/mL with no associated adverse event. Although this small study demonstrated that the high dose was well tolerated, we included only patients who would be at minimal risk of complications, excluding patients with risk factors for hypercalcemia (i.e., malignancy, sarcoidosis, and renal failure).

There are several hypotheses as to why vitamin D supplementation may reduce inflammation in patients with CD, including having been demonstrated to decrease intestinal permeability and increase levels of LL-37, a peptide that may promote wound healing and reduce inflammation in experimental colitis [14, 15]. Our study was not powered to detect a difference in relapse rates, and no significant difference was seen between both groups. Given the large number of withdrawals, we also performed per-protocol analysis and observed a significant reduction in relapse among patients receiving high-dose vitamin D3 ($p = 0.0491$). Significant reductions in CRP were not seen, but this is not surprising given the low baseline levels of CRP recorded in both arms. Other published work has also suggested a potential for vitamin D to improve clinical symptoms. In the only randomized controlled trial to date powered to detect differences in relapse, Jorgensen et al. found a trend toward lower relapse rate in patients treated with one year of 1200 IU daily of vitamin D3 (6/46 patients, 13%) compared to those receiving placebo (14/48 patients, 29%) ($p = 0.06$) [2]. It should be emphasized that the intervention arm from this study used 1200 IU vitamin D3 daily, which was similar to the dose received by patients in our study who were randomized to low-dose therapy. An open-label pilot study found that titrating vitamin D dose to achieve serum 25-OH-vitamin D level above 40 ng/ml (up to a maximum dose of 5000 IU daily of vitamin D3) led to significant reductions in Crohn's disease activity indices (CDAI) and improvements in quality of life among patients with active symptoms of Crohn's disease [16].

Clinically significant improvements in mood were seen in both groups treated with vitamin D; reductions in HADS scores were seen in 82% of patients receiving high-dose vitamin D and 57% of patients receiving low-dose vitamin D. Although the difference between both groups was not statistically significant, our small pilot study was not powered to detect a difference for this outcome. Interestingly enough, use of high-dose vitamin D3 treatment was associated with normalization in mood symptoms in 57% (4/7) of patients with clinical depression and anxiety at baseline. Vitamin D has been demonstrated to improve mood symptoms in other populations as well [17, 18]. Given the high prevalence of anxiety and depressive symptoms among IBD patients [19, 20], further studies exploring use of vitamin D3 therapy in patients with these symptoms are necessary.

Use of vitamin D3 supplementation is cost-effective and may confer additional health benefits, including improvement in bone health and fracture risk [21], and potentially lowering risk of certain malignancies such as colon cancer [4]. Canadian osteoporosis guidelines state that vitamin D levels are sufficient when greater than 75 nmol/l [22], but 25-hydroxy-vitamin D levels greater than 78 nmol/l are needed to avoid increases in parathyroid hormone, and levels greater than 85 nmol/l are needed to maximize calcium and phosphate absorption [23]. It has even been suggested that levels greater than 90 nmol/l are associated with genomic stability and cancer prevention [23]. Since it is unknown if a certain cutoff value is associated with improved clinical remission or mood scores, baseline levels of 25-hydroxy-vitamin D were not used as part of the inclusion or exclusion criteria in this study.

One limitation in our study was the lack of an endoscopic substudy to determine whether mucosal healing rates were impacted in patients receiving high-dose vitamin D therapy. Demonstration of endoscopic improvement in addition to clinical response is now mandated by the Food and Drug Administration for new IBD therapies under investigation [24]. Another drawback was the relatively large number of patients who were lost to follow-up. This could be partly attributed the quaternary nature of the study centre, with long distances required for some patients to attend study visits. The large number of pills that subjects were required to consume daily also likely contributed to some withdrawals due to pill burden. Future studies of higher-dose vitamin D3 should attempt to minimize pill burden if possible. Caution must be used when interpreting the per-protocol analysis of relapse rates, given this large degree of withdrawal, and given this is a secondary analysis. One further limitation of our study was we did not account for the seasonal impact on 25-hydroxy-vitamin D level. However, our study design was such that all patients started the intervention in the spring and finished the intervention in the following spring, so the impact of seasonal variation should have been similar on all subjects.

In conclusion, patients with CD in remission who consume 10,000 IU daily of vitamin D3 were found to have a significant increase in serum 25-hydroxy-vitamin D levels. No difference was seen in remission rates between patients receiving high- and low-dose therapy. Per-protocol analysis demonstrated a lower rate of clinical relapse after one year in patients consuming high-dose vitamin D3 compared to those receiving 1000 IU daily. Patients receiving either dose of vitamin D3 demonstrated improvement in mood, and the dose of 10,000 IU daily showed promise for normalizing mood symptoms in those with clinical anxiety and depression. The number of patients with baseline clinical anxiety and depression was small however, and further investigation of vitamin D3 therapy for improvement in mood is needed. This dose was not associated with adverse events, including no incidences of hypercalcemia. Apart from a larger sample size, future studies of vitamin D supplementation should consider the dose of vitamin D supplemented, the duration of treatment, and the level of 25-OH-vitamin D that is necessary for clinical benefits to become apparent. Studies of patients with active symptoms of Crohn's disease and ulcerative colitis are also warranted to determine whether vitamin D therapy can assist with induction of remission.

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Author contributions NN participated in study design, data analysis, data interpretation, manuscript writing; MC contributed to data collection; RA participated in study design, data analysis, manuscript writing; ZM contributed to data collection; AN took part in data collection; JKM participated in study design, data analysis, data interpretation, manuscript writing.

Compliance with ethical standards

Conflict of interest No authors have any financial interests or connections, direct or indirect, that might raise the question of bias in the work reported in this manuscript.

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