Association of Vitamin D Level With Clinical Status in Inflammatory Bowel Disease: A 5-Year Longitudinal Study

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Association of Vitamin D Level With Clinical Status in Inflammatory Bowel Disease: A 5-Year Longitudinal Study

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OBJECTIVES: **Emerging data suggest that vitamin D has a significant role in inflammatory bowel disease (IBD). Prospective data evaluating the association of vitamin D serum status and disease course are lacking. We sought to determine the relationship between vitamin D status and clinical course of IBD over a multiyear time period.**

METHODS: **IBD patients with up to 5-year follow-up from a longitudinal IBD natural history registry were included. Patients were categorized according to their mean serum 25-OH vitamin D level. IBD clinical status was approximated with patterns of medication use, health-care utilization, biochemical markers of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), pain and clinical disease activity scores, and health-related quality of life.**

RESULTS: **A total of 965 IBD patients (61.9% Crohn's disease, 38.1% ulcerative colitis) formed the study population (mean age 44 years, 52.3% female). Among them, 29.9% had low mean vitamin D levels. Over the 5-year study period, subjects with low mean vitamin D required significantly more steroids, biologics, narcotics, computed tomography scans, emergency department visits, hospital admissions, and surgery compared with subjects with normal mean vitamin D levels ($P<0.05$). Moreover, subjects with low vitamin D levels had worse pain, disease activity scores, and quality of life ($P<0.05$). Finally, subjects who received vitamin D supplements had a significant reduction in their health-care utilization.**

CONCLUSIONS: **Low vitamin D levels are common in IBD patients and are associated with higher morbidity and disease severity, signifying the potential importance of vitamin D monitoring and treatment.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Inflammatory bowel diseases (IBDs) including ulcerative colitis (UC) and Crohn's disease (CD) are characterized by chronic inflammation involving the gastrointestinal tract (1). Although the pathogenesis of IBD is not fully understood, immune dysregulation has a pivotal role (1). Over the past decade, animal and human literature has emerged to support a role of vitamin D in regulating the innate and adaptive immune systems (2–8). In addition to its established role in calcium homeostasis (9), vitamin D directly acts on CD4+ cells, favoring the maturation of T2 helper lymphocyte (Th2) over T1 helper lymphocyte (Th1/Th17) cells (10) and increasing the production of anti-inflammatory cytokines such as interleukin-4 (IL-4), IL-5, and IL-13. Simultaneously, vitamin D acts on dendritic cells, leading to decreased production and differentiation of Th1 cells (10). Consequently, the release of proinflammatory cytokines such as interferon-γ, IL-2, and tumor necrosis factor-α is significantly reduced (10,11). Another important mechanism by which human monocytes eliminate pathogens is autophagy. This occurs through the action of anti-bacterial proteins released locally by vitamin D (11).

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Several epidemiological studies have consistently shown higher prevalence of vitamin D deficiency in patients with IBD (10) and a significant inverse association between vitamin D status and the development of IBD (11). The incidence and prevalence of IBD follow a "North-to-South gradient", with highest incidence and prevalence in colder climates and lowest risks in subjects living closest to the equator (11). This suggests a protective role of vitamin D against inflammation and IBD and is supported by data from the Nurses Health Study that demonstrate lower incidence of IBD in subjects with high baseline 25-OH vitamin D plasma levels (11).

Despite these advances, there are no long-term prospective studies evaluating the association of vitamin D status with clinical course in IBD. The aim of this study was to determine the relationship between mean vitamin D status over a multiyear time period and the clinical course in a large cohort of IBD patients who were followed prospectively in a tertiary referral IBD center.

METHODS

Patients

The Inflammatory Bowel Disease Center at the University of Pittsburgh Medical Center maintains a consented, longitudinal IBD natural history registry. Our registry includes demographic, laboratory, clinical, endoscopic, radiological, pathological, and other clinical data of enrolled patients and is updated routinely through Information Technology support. We analyzed deidentified longitudinal data from patients with definitive IBD diagnosis who were seen at our center during the 5-year period extending from 1 January 2009 to 31 December 2013. Study subjects had varying follow-up duration. Basic demographic data including age, gender, and smoking status were recorded. As part of their usual IBD care, patients underwent routine testing for serum 25-OH vitamin D levels using liquid chromatography-tandem mass spectrometry. Vitamin D levels were checked in all patients on enrollment. In subjects who had low vitamin D levels, repeat testing was conducted at their 3–6-monthfollow-up period. As for those with normal levels, levels were checked on a 6-month to yearly basis. Past studies showed that serum 25-OH vitamin D levels reflect vitamin D body status with excellent precision given its long half-life (15 days) (12). Therefore, mean vitamin D levels were used primarily for analysis, as this is the most precise approximation of the body stores of vitamin D during the study duration. Those who had vitamin D deficiency and insufficiency received supplements. To standardize approach to vitamin D monitoring and supplementation, IBD nurses follow a quality improvement protocol formulized by IBD specialists at the University of Pittsburgh Medical Center. This protocol involves prescribing 50,000 IU of weekly or biweekly vitamin D supplements for at least 12 weeks followed by repeat testing and supplementation, when needed. Patients were categorized by the mean serum 25-OH vitamin D level over the 5-year time period in accordance with the American and European Societies of Endocrinology. 25(OH) vitamin D concentrations of <50 nmol/l or 20 ng/ml were consistent with vitamin D deficiency, whereas 25(OH) vitamin D concentrations of 51–74 nmol/l or 21–29 ng/ml indicated insufficiency. Concentrations >30 ng/ml or >75 nmol/l were considered to be normal or sufficient (12). To simplify interpretation of data, patients with vitamin D deficiency and insufficiency were clustered together and constituted the "low vitamin D group". Patients with concentrations >30 ng/ml constituted the "normal vitamin D group". However, we conducted separate analysis that was limited to vitamin D levels at baseline. This was to exclude the bias introduced by differential supplementation of vitamin D and potential variance of vitamin D levels from one year to another. In this analysis, we monitored health-care utilization among three groups: (1) those with vitamin D deficiency, (2) subjects with vitamin D insufficiency, and (3) subjects with normal levels.

To examine vitamin D status across different age groups, we used the World Health Organization (13) age classification, which categorizes individuals who are <45 years as young, between 45 and 65 years as middleaged, and >65 years as senior. We also examined vitamin D status across disease type (UC vs. CD) and anatomic distribution. CD and UC were characterized according to the Montreal classification (14). We also monitored smoking status, which we defined as any active use of tobacco during the study period.

To approximate IBD clinical status, we monitored patterns of medication use, health-care utilization, biochemical markers of inflammation, and disease activity scores. Monitored prescriptions for relevant medications included steroids (prednisone), immunomodulators (6-mercaptopurine, azathioprine, and methotrexate), anti-tumor necrosis factor agents (infliximab, adalimumab, certolizumab, and golimumab), and narcotics. Narcotic use was defined as requiring one or more prescription of opioids that was for IBD-related pain regardless of the count of pills.

We approximated health-care utilization by monitoring the number of phone calls recorded in the electronic medical record for an IBD-related issue. Moreover, the frequency of IBD-related emergency department (ED) and clinic visits, computed tomography (CT) scan imaging studies, hospital admissions, and the need for surgery were documented for analysis. Validated disease activity scores (Harvey–Bradshaw index (HBI) for CD (15) and UC disease activity index (UCAI) for UC) (16) were documented for comparison between the low and normal vitamin D study groups. In addition, health-related quality of life was assessed using short inflammatory bowel disease questionnaire (SIBDQ) (17). We also analyzed pain subscores based on the response to question 4 of the SIBDQ, which asks "How often during the last 2 weeks have you been troubled by abdominal pain?". This subscore has been validated formerly by Ramos-Rivers *et al.* (18) and is a 1- to 7-point scale, where 7 stands for "none of the time" and 1 stands for "all of the time". Finally, biochemical markers of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate) were included for comparison.

Statistical analysis

Statistical analysis was performed using STATA for Windows, Rel. 13.0. 2004 (STATA, Chicago, IL). Study outcomes were assessed using Fisher's exact test, analysis of variance, or the χ^2 test with Yates correction for discrete variables and Student's *t*-test

as appropriate. *P* value of <0.05 indicated statistical significance. To identify whether vitamin D status was an independent risk factor for increased disease activity, pain, health-care utilization, and poorer quality of life, we conducted multivariate analyses controlling for age, gender, smoking status, disease status (CD or UC), duration since disease diagnosis, and the use of medications. Specifically, zero-inflated Poisson regression analysis was conducted as the outcome (health-care utilization) has a Poisson distribution and the data were analyzed in the count (contingency table) approach. We also conducted Kaplan–Meier survival analysis of first surgical procedure during the study duration in those who had steadily normal vitamin D levels compared with those who had steadily low vitamin D levels excluding subjects who received vitamin D supplementation. The Institutional Review Board at University of Pittsburgh Medical Center and University of Pittsburgh approved this study (PRO12110117).

RESULTS

In total, 965 IBD patients (61.9% CD, 38.1% UC) formed the study population. **Table 1** shows the demographic, clinical characteristics, and data on vitamin D testing and status in the study population.

Overall, the anatomical distribution of CD and UC was similar to the trend seen in the general IBD population (**Table 2**). As for CD behavior, 50.3% of the CD cohort had inflammatory disease (B1), 21.9% had stricturing disease (B2), 19.3% had penetrating disease (B3), 8.5% had combined disease phenotypes (B2 plus B3), and 15.8% had perianal disease. At study entry, 8.9% of the study population was vitamin D deficient, and 33.1% had vitamin D insufficiency. At study conclusion, 47 subjects (4.9%) had vitamin D deficiency, 228 had vitamin D insufficiency (23.6%), and 71.5% had normal vitamin D levels. Of those who received supplements, 67.9% achieved normal vitamin D levels at study conclusion.

The prevalence of low vitamin D levels was higher in males compared with females (*P*<0.0001) (**Table 2**). Young adults had the highest prevalence of low vitamin levels compared with middle-aged patients and seniors (*P*=0.005) (**Table 2**). The mean vitamin D levels were 35.2 ng/ml (s.d. 12.0) in patients with CD and 35.7 ng/ml (s.d. 11.6) in those with UC (*P*=0.52). No difference in the prevalence of low vitamin D between CD and UC patients was found (*P*=1.0) (**Table 2**). Similarly, there was no statistical difference in vitamin D levels across the groups of CD or UC location: (*P*=1.0 and 0.9, respectively). In the low vitamin D group, the mean disease duration was no different compared with the normal D group (*P*=0.6) (**Table 2**).

Over the 5-year study period, significantly more CD and UC patients with low vitamin D levels required steroids, initiation of biologics, and narcotics for pain control compared with those with normal vitamin D levels (**Table 3**). In those who required narcotics, the mean frequency of prescriptions over the 5-year study period was 7.7 (s.d. 11.0) prescriptions per individual in the low vitamin D group compared with 5.3 (s.d. 8.1) in the normal vitamin D group (*P*=0.04). Similarly, the frequency of steroid prescriptions was significantly higher in the low vitamin D group compared with the normal vitamin D group (6.3 (s.d. 7.7) vs. 4.7 (s.d. 5.4), *P*=0.03). Immune modulator use was similar in CD subjects (66.4% vs. 67.2%, *P*=0.9) but was significantly higher in UC subjects with low vitamin D levels compared with those with normal vitamin D levels (67.6% vs 42.8%, *P*<0.0001).

In addition, the low vitamin D group subjects in both diseases (UC and CD) received more frequent computed tomography scan imaging, ED visits, hospitalizations, and surgery compared with those with normal mean vitamin D levels (**Table 3**).

In comparing patterns of elevated inflammatory biomarkers, there was no difference in CRP elevation (55.2% vs. 49.9%, *P*=0.6) and abnormal erythrocyte sedimentation rate (60.5% vs. 57.4%, *P*=0.8) between the low and normal vitamin D groups. Moreover, there was no statistical difference in the frequency of phone calls or clinic visits (*P*=0.2 and 0.3, respectively).

Finally, pain subscores were significantly worse among CD and UC subjects with low vitamin D levels, indicating more frequent abdominal pain, compared with the normal vitamin D group (**Table 3**). Moreover, both CD and UC patients with low vitamin D had worse disease activity with higher HBI (*P*<0.0001) and UCAI scores (*P*<0.01), respectively. In addition, they had worse quality of life as is indicated by lower mean SIBDQ scores (*P*=0.06 and 0.002 for CD and UC, respectively) (**Table 3**).

Table 1. Demographics and vitamin status of study patients

Study population	965
Mean age (years, s.d.)	44 (10.1)
Females (%)	52.3
Total vitamin D tests (*N*)	4780
Mean disease duration (years, s.d.)	16.3 (5.6)
Mean study follow-up (years, s.d.)	3.4 (1.0)
Mean vitamin D tests per study individual (*N*, s.d.)	5.0 (1.8)
Mean vitamin D tests per study individual per study year (*N*, s.d.)	1.5 (0.4)
Prevalence of low vitamin D status at study entry (%)	42
Prevalence of low vitamin D status at study conclusion (%)	25.6
Percentage receiving vitamin D supplements (%)	46.5
Mean vitamin D prescription per individual (*N*, s.d.)	1.8 (0.6)
New diagnosis at enrollment (% of study cohort)	31.7
In clinical remission at enrollment (% of study cohort)	46.5
Started on new medication within 1 year before enrollment (% of study cohort)	28.9
C diff infection within 1 year before enrollment (% of study cohort)	7
Required surgery within 1 year before enrollment (% of study cohort)	6.4
Need for steroids within 1 year before enrollment (% of study cohort)	12.3

C diff, *Clostridium difficile*.

Table 2. Relationship between baseline vitamin D and clinical characteristics of study patients

	Low vitamin D	Normal vitamin D	*P* value
Age			0.005
Young[a] (%)	34.8	65.2	—
Middle aged[a] (%)	28.4	71.6	—
Senior[a] (%)	19.4	80.6	—
Gender			<0.0001
Female (%)	61.5	38.5	
Male (%)	75.9	24.1	
Ethnicity (% Caucasian)	91.5%	92.1%	1.0
Smoking status			0.6
Yes (%)	24.6%	25.9%	
Disease type			1
CD (%)	30.0	70.0	
UC (%)	29.9	70.1	
Disease location for CD			0.8
Upper GI (%)	31.2	68.8	—
Ileal (%)	30.5	69.5	—
Ileocolonic (%)	29.8	70.2	—
Colonic (%)	29.9	70.1	—
Disease location for UC			0.9
Proctitis (%)	30.1	69.9	—
Left-sided colitis (%)	29.7	70.3	—
Extensive colitis (%)	29.9	70.1	—
Disease duration in years (s.d.)	16.6 (10.2)	16.2 (10.4)	0.6

CD, Crohn's disease; GI, gastrointestinal; UC, ulcerative colitis.
[a]Young: <45 years; middle aged: 45–65 years; senior: >65 years.

In addition to analyzing HBI and UCAI activity scores as continuous variables, we treated them as categorical values with cutoffs of >4 signifying clinically active disease, to determine the relative risk of active disease in low vitamin D. The relative risk for active disease (HBI >4) was 1.9 (P=0.0003). Similarly, the relative risk for clinically active disease in UC subjects with low vitamin D was 1.8 (P=0.0375).

Analysis of outcomes based on baseline vitamin D levels

To account for the potential bias introduced by vitamin D supplementation and given the potential variance of vitamin D level from one year to another, we performed separate analysis of vitamin D levels at study entry. We also analyzed the outcomes at baseline (year 1 of enrollment), as it is more appropriate for hypothesis testing than analyzing outcome at study conclusion. For the purpose of this analysis and to illustrate any dose–response pattern in health-care utilization, the study cohort was divided into three groups: vitamin D deficient, vitamin D insufficient, and normal vitamin D. Results are shown in **Supplementary Table 1** online.

Over the course of the 5-year duration, 69 of the 356 subjects with normal vitamin D levels (19.4%) required surgery, as opposed to 47 of the 161 subjects with low vitamin D levels (29.2%). Kaplan–Meier survival analysis showed a significant difference in the surgery survival curves between IBD patients with normal or low vitamin levels during the study period (P=0.001) (**Figure 1**).

Analysis of outcomes based on disease severity

To control for the potential confounding effect of disease severity at presentation, we conducted subgroup analysis of patients who were in clinical remission at study enrollment. In total, 46.5% of the cohort subjects were in clinical remission. When stratified by disease type, 43.2% of the CD subjects and 52% of the UC subjects were in clinical remission at study enrollment.

In both diseases, outcomes were worse in subjects who had active disease at baseline compared with those who were in remission (**Table 4**). There was also significantly lower prevalence of vitamin D deficiency in subjects who were in remission.

Moreover, and to control for the potential role of vitamin D, we conducted another subgroup analysis of subjects who were in remission at enrollment and stratified them by vitamin D status. Of the 449 subjects who were in remission at enrollment, 98 (21.8%) had low vitamin D levels during the study follow-up. Compared with the subjects who had normal vitamin D levels and were in remission, subjects with low vitamin D levels required more steroid use (51% vs. 37.3%) (P=0.02), had worse disease scores (3.1 vs. 1.6) (P<0.0001), and required more IBD-related surgery (33.9% vs. 22.4%) (P=0.04).

Effects of seasonality

Previous literature suggests large variability in vitamin D levels based on seasonality and differential exposure to sunshine (lower in colder months) (19). To control for bias introduced by seasonality, we reviewed the dates on which vitamin D levels were checked at all study points. We found that there was a higher likelihood for vitamin D level to be low if checked in winter or fall and higher likelihood to be normal if checked in spring or summer (**Figure 2**). Nonetheless, the same number of tests were ordered in the spring and summer (50%) period compared with the winter and fall period (50%) (**Figure 2**).

Moreover, we conducted a subgroup analysis of subjects who had active disease to investigate whether the higher vitamin D deficiency prevalence was related to ordering more tests in the fall and winter period. This group of 516 patients underwent slightly more testing in the spring/summer than they did in the fall/winter season (50.8% vs. 49.2%).

Multivariate analysis

The results of multivariable analysis are presented in **Table 4**. The normal vitamin D group had a mean pain subscore and a mean SIBDQ score higher compared with the low vitamin D group

Table 3. Medication use, disease activity scores, quality of life, and health-care utilization during the study period in CD and UC patients stratified by vitamin D status

	CD (*n*=597)			UC (*n*=368)		
	Normal vitamin D (*n*=417)	Low vitamin D (*n*=180)	*P* value	Normal vitamin D (*n*=257)	Low vitamin D (*n*=111)	*P* value
Prednisone use (%)	43.2	52.2	0.048	50.2	65.8	0.006
Mean prednisone prescriptions	2.1	2.2	0.9	1.4	1.8	0.7
Biologics use (%)	46.3	60.8	0.002	21.4	40.5	0.0002
Immune modulators use (%)	66.4	67.2	0.9	42.8	67.6	<0.0001
Mean narcotic prescriptions	2.2	2.4	0.9	2.0	2.7	0.1
Narcotics use (%)	35.5	43.9	0.05	17.1	40.5	<0.0001
HBI score for CD or UCAI for UC (mean, 95% CI)	3.9 (3.4–4.4)	5.4 (5.0–5.8)	<0.0001	3.6 (3.3–3.9)	4.8 (4.3–5.3)	<0.01
Pain subscore[a] (mean, s.d.)	5.8 (0.4)	4.4 (0.4)	<0.0001	5.4 (0.4)	3.9 (0.4)	<0.0001
SIBDQ score[b] (mean, s.d.)	51.3 (5.2)	48.5 (4.3)	0.06	54.0 (2.4)	49.6 (2.2)	0.002
ED visits (mean, 95% CI)	1.9 (1.5–2.3)	5 (3.5–6.4)	<0.0001	2.1 (1.7–2.5)	4 (3.2–4.8)	<0.0001
CT scans (mean, 95% CI)	1.2 (0.9, 1.5)	1.8 (1.6–2.0)	0.04	0.7 (0.4–1.0)	1 (0.8–1.2)	0.1
Hospitalizations (mean, 95% CI)	1.4 (1.0–1.8)	2.7 (2.1–3.2)	<0.0001	1.2 (1.0–1.4)	1.9 (1.5–2.3)	0.03
Mean surgery/person	1.4	2.8	<0.0001	1.1	1.6	<0.0001
IBD-related surgery (%)	55.6	71.7	0.0003	19.8%	38.7%	0.0002

CD, Crohn's disease; CI, confidence interval; CT, computed tomography; ED, emergency department; HBI, Harvey–Bradshaw index; IBD, inflammatory bowel disease; SIBDQ, short inflammatory bowel disease questionnaire; UCAI, ulcerative colitis activity index; UC, ulcerative colitis.

[a]Lower score indicates more pain.

[b]Lower score indicates higher disease activity.

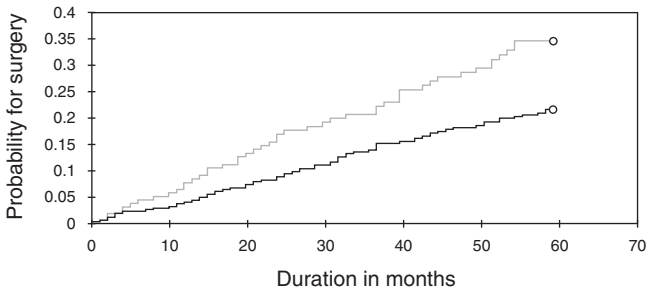

Figure 1. Kaplan–Meier surgery survival curves in inflammatory bowel disease patients evaluated in clinic, stratified by vitamin D status. Black line = normal vitamin D group; grey line = low vitamin D group.

(*P*<0.001 and *P*=0.005, respectively). As for CD activity, a linear regression model showed that the normal vitamin D group had a mean HBI score that was lower compared with the low vitamin D group (*P*<0.001). The same trend was noted in UC patients; the normal vitamin D group had a mean UCAI score lower compared with the low vitamin D group (*P*<0.032). Finally, to assess health-care utilization (computed tomography scans, ED visits, hospitalizations, surgeries), zero-inflated Poisson regression model analysis was conducted. The model showed that the normal vitamin D group used the health-care system less (0.44 times) than the low vitamin D group (*P*<0.001) (**Table 5**).

Subgroup analysis

To examine the effect of vitamin D supplementation on health-care utilization over the 5-year study period, we analyzed data of individuals who had a 5-year follow-up, received vitamin D supplements, had similar disease activity scores through study period, and were on the same IBD maintenance therapy throughout the study. The latter two criteria were to control for the effects of medication changes and disease activity on health-care utilization. One hundred and thirty-eight subjects met the criteria for this subgroup analysis. The mean vitamin D levels were 24.6, 27.1, 31.8, 37.6, and 43.3 ng/ml in years 2009, 2010, 2011, 2012, and 2013, respectively. Yearly health-care utilization scores were calculated by summing the number of ED visits, hospital discharges, computed tomography scan imaging, surgeries, and clinic visits each year. Mean health-care utilization scores were 11.4, 9.4, 8.9, 8.6, and 6.1 for years 2009, 2010, 2011, 2012, and 2013, respectively. Linear regression analysis showed a negative correlation between vitamin D levels and health-care utilization, as signified by an R^2 of 0.9. The coefficient for this correlation was 0.2 (**Figure 2**). For comparison, subjects with low vitamin D levels who did not receive vitamin D supplement prescriptions were followed. In general, their vitamin D levels were lower and they used the health-care system more often (**Figure 3**). Both groups had comparable distribution by age, gender, disease type, and the use of

Table 4. Comparison between subjects in remission and subjects with active disease at baseline

	CD (*n*=597)			UC (*n*=368)		
	In remission (*n*=258)	Active disease (*n*=339)	*P* value	In remission (*n*=191)	Active disease (*n*=177)	*P* value
Low vitamin D (%)	22.9	35.4	0.001	20.4	40.7	<0.0001
Steroids use (%)	37.2	52.5	0.0003	44.5	67.2	<0.0001
HBI score for CD or UCAI for UC (mean, s.d.)	2.2 (0.4)	6.0 (0.6)	<0.0001	1.8 (0.3)	6.2 (0.6)	<0.0001
Hospitalizations (mean, s.d.)	0.8 (0.2)	2.6 (0.5)	<0.0001	0.5 (0.1)	2.4 (0.6)	<0.0001
IBD-related surgery (%)	41.5	74.9	<0.0001	17.8	33.9	0.0005

CD, Crohn's disease; HBI, Harvey–Bradshaw index; IBD, inflammatory bowel disease; UC, ulcerative colitis; UCAI, ulcerative colitis activity index.

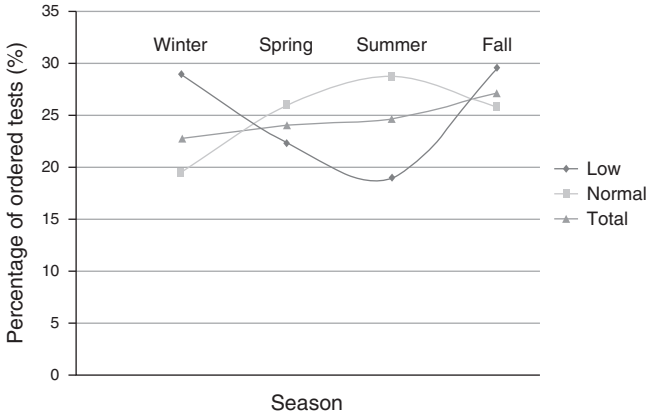

Figure 2. Frequency of vitamin D testing in inflammatory bowel disease patients by seasonality.

Table 5. Determinants of vitamin D status in the multivariate analysis

	Mean or risk ratio (95% confidence intervals)	*P* value
Mean difference in pain scores between the study groups	0.4 (0.2, 0.6)	<0.001
Mean difference in SIBDQ scores between the study groups	2.1 (0.6, 3.5)	0.005
Mean difference in HBI scores (in CD) between the study groups	1.1 (–1.8, –0.5)	<0.001
Mean difference in UCAI scores (in UC) between the study groups	1 (–1.9, –0.1)	<0.032
Health-care utilization risk ratio	0.7 (–0.39, –0.27)	<0.001

CD, Crohn's disease; HBI, Harvey–Bradshaw index; SIBDQ, short inflammatory bowel disease questionnaire; UC, ulcerative colitis; UCAI, ulcerative colitis activity index.

medications at baseline (*P* values were 0.9, 0.8, 0.9, and 0.7, respectively).

DISCUSSION

Cross-sectional studies have examined associations between vitamin D status and IBD outcomes. Ulitsky *et al.* (20) reported that vitamin D deficiency was associated with increased disease activity in CD and UC and worse quality of life in CD but not in UC. In other studies, vitamin D was inversely associated with disease activity (21), increased risk of surgery and hospitalizations (22), and a higher need for steroids (23).

All these studies, however, were cross-sectional and failed to examine the long-term association of vitamin D levels with health outcomes and had limitations in sample size and the number of studied outcomes.

By conducting a multiyear cohort study in just under one thousand IBD patients and following them over a long period of time, we aimed to verify the findings of past cross-sectional studies and examine other IBD outcomes that were not previously evaluated. Moreover, we focused upon health-care utilization, given the importance of containing health-care resources. Finally, our study design allowed for evaluating the impact of vitamin D supplementation on health outcomes in vitamin D-deficient subjects, one thing that would not be feasible with a cross-sectional study design. Although a randomized controlled study has, in general, a stronger epidemiological impact, conducting such a study would not have been ethical, as it potentially involves withholding an important treatment/therapy in individuals who were diagnosed with vitamin deficiency.

Our results confirmed the findings of several previous studies that reported a high prevalence of vitamin D deficiency in subjects with IBD (21–24). To simplify analysis and conclusions of the study and as the management of vitamin D insufficiency and deficiency is virtually the same, we clustered them together. However, even when stratifying by World Health Organization classification, a dose–response trend was seen across the majority of the study outcomes, adding more plausibility to our findings.

Although IBD subjects have higher prevalence of vitamin D deficiency compared with the general population, the major contributing causes remain unclear. Potential mechanisms include decreased vitamin D dietary intake, lower sun exposure, decreased

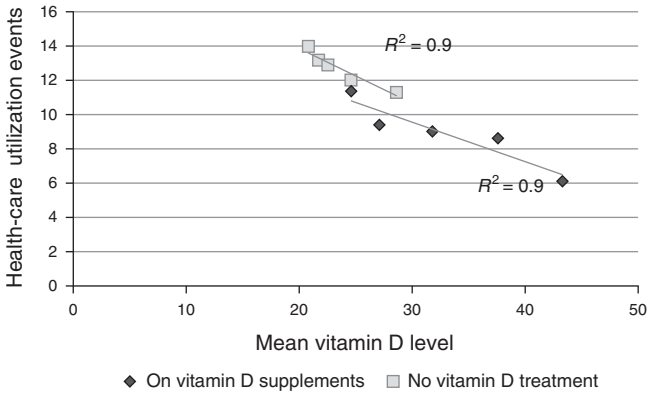

Figure 3. Effects of vitamin D supplementation on health-care utilization by inflammatory bowel disease patients.

absorption from ongoing inflammation, and decreased bile salt acid absorption in subjects who undergo ileocecal resection (20). Our study suggests that decreased absorption from small bowel inflammation and/or decreased bile acid absorption are less likely to be major factors. In fact, the prevalence of low vitamin D was similar in those who had ileocecal valve resection and those who did not. Moreover, patients with UC had similar prevalence of vitamin D deficiency compared with CD patients. Finally, CD patients with isolated colonic involvement had similar vitamin D status compared with those who had small bowel or ileocolonic disease.

Another important finding of our study was that young males had the highest risk of vitamin D deficiency. This is contrary to a past study that reported a negative association between vitamin D levels and age (25). Consumption of over-the-counter and prenatal vitamins could be one factor. Moreover, sampling error is another potential cause given that only 87 subjects (9% of our cohort) were seniors. Moreover, genetic and hormonal mechanisms could explain our finding, as estrogen has been shown to protect against vitamin D deficiency (26,27). Finally, lifestyle and dietary habits/trends could be other contributing factors.

Our study showed that subjects with low vitamin D require biologics, steroids, and narcotics more often. Moreover, low vitamin D status was associated with worse disease activity and pain, and poorer quality of life. There were no significant differences in biomarkers of inflammation between the two study groups.

After controlling for covariates, subjects with low vitamin D levels used the health-care system 44% more than those with normal vitamin D. This has significant cost implications and should be followed by cost-analysis studies to estimate possible health-care expenditure reduction with vitamin D supplementation.

Evidence suggests that vitamin D has more than an incidental role in IBD. There are plausible biological mechanistic links between low vitamin D levels and severity of colitis in animal models (both *in vivo* and *in vitro*) (2–4), as well as in humans (5). Moreover, one study has shown that vitamin D supplementation in patients with low vitamin D is associated with improved disease outcomes (28). This observation is supported by our results showing a significant decrease in health-care utilization in subjects with higher vitamin D levels (**Figure 1**). Nonetheless, our data are not sufficient to claim a cause–effect relationship yet because of the known limitations of observational data in general. Coming years will reveal the findings of ongoing clinical trials, which are evaluating the effects of high-dose vitamin D supplementation in IBD patients (see https://clinicaltrials.gov/).

There are limitations to our investigation. First, the study was conducted in a tertiary center in Pittsburgh, Pennsylvania, the second cloudiest major city in the United States (http://www.ncdc.noaa.gov); hence, the population might not be representative of the US population. Although we believe that the prevalence of vitamin D deficiency and poor IBD outcomes will not be reproducible (probably less) in other areas of the world where there is more sunshine given the tight relationship between the geographical location and vitamin D levels, we expect the correlation between the vitamin D levels and the clinical status to hold strong regardless of the location given the accumulating literature and our study findings. Another limitation was that many patients lacked sufficient available endoscopic findings to investigate the association between vitamin D status and the degree of inflammation. Similarly, we lacked bone mass densitometry studies and fecal calprotectin levels (29) on most of the study subjects. Moreover, the findings of our study could be due to reverse causation—i.e., IBD subjects with poorly controlled disease may be at higher risk of low vitamin D status. In addition, it is possible that low vitamin D levels and poor outcomes are both confounded by non-compliance with medical treatment. However, non-compliance alone is less likely to explain all our findings as subjects with low vitamin D made the same number of phone calls and clinic visits compared with those with normal vitamin D. Moreover, most of the subjects who received vitamin D supplements had at least a 15-point increase in their vitamin D levels at study conclusion, which suggests compliance with treatment. Finally, although seasonality could be a potential cause for lower vitamin D levels, our testing for vitamin D was consistent throughout the seasons, especially in subjects who had worse clinical outcomes.

In conclusion, low vitamin D levels are common in IBD. IBD patients with low mean vitamin D levels have worse disease activity, worse pain, higher need for biologics, steroids and narcotics, and increased health-care utilization. Vitamin D status is an independent risk factor for worse IBD outcomes. Vitamin D supplementation also appears to be associated with improvement in health-care utilization, which is reflective of improved overall health. We eagerly await the results of clinical studies in process to understand more whether vitamin D supplementation will have an adjunct role in ameliorating IBD activity and symptoms.

CONFLICT OF INTEREST

Writing assistance: None.

Specific author contributions: Toufic A. Kabbani: enrollment of subjects, acquisition of data, analysis and interpretation of data, and drafting of manuscript. Ioannis E. Koutroubakis: acquisition of data, analysis and interpretation of data, drafting of manuscript, and critical review of manuscript. Robert E. Schoen: critical review of manuscript. Claudia Ramos Rivers: enrollment of subjects and acquisition of data. Nilesh Shah: statistical analysis. Jason Swoger:

acquisition of data. Miguel Regueiro: acquisition of data. Arthur Barrie: acquisition of data. Marc Schwartz: acquisition of data. Jana Hashash: acquisition of data. Leonard Baidoo: acquisition of data. Michael Dunn: acquisition of data. David G. Binion: acquisition of data, analysis and interpretation of data, drafting of manuscript, critical review, and final approval of the manuscript.

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Potential competing interests: Ioannis Koutroubakis: consulting/advisory board for Abbvie and MSD; Miguel Regueiro: has served as a consultant for Abbvie, Janssen, Shire, Takeda, and UCB. David Binion: consulting/advisory board for Abbvie, Janssen, FDA Safety Board of UCB Pharma, and grant support from Janssen, Merck, and UCB Pharma. The other authors declare no conflict of interest.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Low vitamin D is common in patients with inflammatory bowel disease (IBD).
- ✓ Epidemiologic data suggests a role for low vitamin D and the development of IBD.
- ✓ Low vitamin D is associated with increased risk of surgery in IBD.
- ✓ There is limited data suggesting low vitamin D is associated with increased disease activity in IBD, particularly Crohn's disease.

WHAT IS NEW HERE

- ✓ We used a prospective, longitudinal, observational, IBD natural history database to conduct a multiyear cohort study to evaluate the relationship between serum vitamin D status and clinical course over a 5 year time period in 965 patients.
- ✓ IBD patients with low mean vitamin D status (29.9%) had more steroid exposure, anti-TNF biologic requirement, narcotics, computed tomography (CT) scans, emergency department visits, hospital admissions and surgery compared with IBD patients with normal mean vitamin D levels.
- ✓ IBD patients with low vitamin D over 5 years had more chronic abdominal pain, disease activity and worse quality of life.
- ✓ IBD patients who received supplementation and corrected vitamin D status had a significant reduction in healthcare utilization.

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