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Retrospective Study

Prevalence and factors associated with vitamin C deficiency in inflammatory bowel disease

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Abstract

BACKGROUND

Patients with inflammatory bowel disease (IBD) are prone to several nutritional deficiencies. However, data are lacking on vitamin C deficiency in Crohn's disease (CD) and ulcerative colitis (UC) patients, as well as the impact of clinical, biomarker and endoscopic disease severity on the development of vitamin C deficiency.

AIM

To determine proportions and factors associated with vitamin C deficiency in CD and UC patients.

METHODS

In this retrospective study, we obtained clinical, laboratory and endoscopic data from CD and UC patients presenting to the IBD clinic at a single tertiary care center from 2014 to 2019. All patients had an available plasma vitamin C level. Of 353 subjects who met initial search criteria using a cohort discovery tool, 301 ultimately met criteria for inclusion in the study. The primary aim described vitamin C deficiency (≤ 11.4 μmol/L) rates in IBD. Secondary analyses compared proportions with deficiency between active and inactive IBD. Multivariate logistic regression analysis evaluated factors associated with deficiency.

RESULTS

Of 301 IBD patients, 21.6% had deficiency, including 24.4% of CD patients and 16.0% of UC patients. Patients with elevated C-reactive protein (CRP) (39.1% *vs* 16.9%, $P < 0.001$) and fecal calprotectin (50.0% *vs* 20.0%, $P = 0.009$) had signifi-

cantly higher proportions of deficiency compared to those without. Penetrating disease (P = 0.03), obesity (P = 0.02) and current biologic use (P = 0.006) were also associated with deficiency on univariate analysis. On multivariate analysis, the objective inflammatory marker utilized for analysis (elevated CRP) was the only factor associated with deficiency (odds ratio = 3.1, 95% confidence interval: 1.5-6.6, P = 0.003). There was no difference in the presence of clinical symptoms of scurvy in those with vitamin C deficiency and those without.

CONCLUSION

Vitamin C deficiency was common in IBD. Patients with elevated inflammatory markers and penetrating disease had higher rates of vitamin C deficiency.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Vitamin C deficiency; Scurvy; Malnutrition

Core Tip: This study aimed to determine proportions and factors associated with vitamin C deficiency in inflammatory bowel disease (IBD) patients. In 301 patients, 21.6% had vitamin C deficiency, including 24.4% of Crohn's disease and 16.0% of ulcerative colitis patients. Patients with elevated C-reactive protein (39.1% *vs* 16.9%) and fecal calprotectin (50.0% *vs* 20.0%) had higher proportions of deficiency compared to those without, as did patients with penetrating disease (36.2% *vs* 20.8%). This study provides the largest data on vitamin C deficiency in IBD, and demonstrates that deficiency is common in this population, particularly those with markers of active luminal or penetrating disease.

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INTRODUCTION

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract that affect over 1.5 million people in the United States alone[1,2]. Several nutritional deficiencies are well described in patients with IBD, the most common being iron, vitamin B12, vitamin D, zinc, and calcium[3-7]. However, far less literature exists on vitamin C (ascorbic acid) deficiency in this population. While the prevalence of scurvy - the clinical manifestations of vitamin C deficiency - has largely declined in the 21st century, up to 7% of the United States population still possesses vitamin C deficiency. The risk of deficiency is particularly increased in smokers, obese patients, and patients from low-income backgrounds[8]. Among those also at risk are patients with poor vitamin C intake and malabsorptive processes.

Traditionally, in IBD patients, vitamin C deficiency is thought to originate from insufficient consumption, malabsorption, and altered metabolism of vitamin C. Although not routinely recommended, many IBD patients adhere to low-residue diets to decrease gut motility and bacterial fermentation of fiber. Unfortunately, several regimens exclude fresh fruit and vegetables, the main dietary sources of vitamin C[9]. Inadequate consumption is often compounded by malabsorption of vitamin C in these patients. Ascorbate is primarily absorbed in the jejunum and ileum, which are often affected in CD[10]. In addition, patients with IBD have been shown to have polymorphisms in genes encoding vitamin C transporters necessary for vitamin C uptake[11,12]. Lastly, tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine often elevated in IBD, also downregulates transcription of transporters necessary for vitamin C uptake[13,14].

Vitamin C deficiency can lead to impaired uptake and utilization of iron, poor wound healing, and bleeding[15,16]. The diagnosis of vitamin C deficiency can be all the more challenging to make in patients with IBD, as many nonspecific symptoms of scurvy - fatigue, arthralgias, and cutaneous manifestations - can confound systemic symptoms of CD and UC. Prior studies of patients with IBD have described inadequate vitamin C intake and suboptimal serum vitamin C levels in 22%-70% and 15%-84%, respectively[9,17-20]. Notably, these studies have been small, excluded patients with UC, and occurred prior to the advent of biologic medications. Importantly, cohorts lacked data on clinical, biomarker and endoscopic measures of disease activity to assess for their impact on vitamin C deficiency.

IBD patients are at risk for malnutrition and vitamin C deficiency is an easily reversible condition. Thus, it is essential to understand the prevalence of and factors associated with vitamin C deficiency in this population to better identify those at risk. For this reason, this study aimed to determine rates of vitamin C deficiency in patients with CD and UC and investigate potential factors associated with the development of vitamin C deficiency in this population.

MATERIALS AND METHODS

Patient population

Data were extracted from chart review of patients presenting to the IBD clinic at a single tertiary institution from 2014 to 2019. Patients were identified using a cohort discovery tool (Informatics for Integrating Biology and the Bedside, National Center for Biomedical Computing, Partners HealthCare System, Boston, Massachusetts) at Weill Cornell Medicine, New York. Search criteria included age 18 years and older, diagnosis of CD or UC, and a plasma vitamin C measurement drawn from 2014 to 2019. International Classification of Diseases 10th edition codes were used to identify patients with CD (K50.x) and UC (K51.x). Exclusion criteria included lack of a CD or UC diagnosis, plasma vitamin C level, or IBD-related visit at the time that plasma vitamin C measurement was performed. Three hundred fifty-three subjects matched initial search criteria. In patients with multiple plasma vitamin C levels, the lowest value and associated visit were utilized. This study was conducted retrospectively from data obtained for clinical purposes. The study was approved by the institutional review board at Weill Cornell Medicine, who confirmed that no ethical approval was required.

Data extraction

We extracted covariates readily available in the electronic medical record. Baseline characteristics were collected, including age, sex, race, body mass index (BMI), smoking history, type of IBD (CD or UC), disease duration and prior IBD-related surgeries (*i.e.*, total proctocolectomy, ileocolonic resection, small bowel resection, *etc.*). Endoscopic scores - within six months of plasma vitamin C level assessment - were collected when available. Disease location and behavior were defined by the Montreal classification for IBD[21]. Patients were evaluated for current and prior IBD medications, including biologic agents such as TNF-α inhibitors (infliximab, adalimumab, golimumab, and certolizumab pegol), vedolizumab, and ustekinumab. Additional laboratory values collected within one week of plasma vitamin C levels were included in the analysis. When available, C-reactive protein (CRP), iron, transferrin saturation, ferritin, vitamin B12, vitamin D, 25-hydroxy, and fecal calprotectin were obtained. Iron deficiency was defined as ferritin < 30 ng/mL and transferrin saturation < 16% in those with quiescent disease and ferritin < 100 ng/mL and transferrin saturation < 16% in those with active disease[22]. Vitamin B12 deficiency was defined as serum vitamin B12 level < 200 pg/mL or < 148 pmol/L[7]. Vitamin D deficiency or insufficiency was defined as serum vitamin D, 25-hydroxy level ≤ 20 ng/mL [23]. From the electronic medical record, we also extracted data on symptoms typically associated with vitamin C deficiency (*i.e.*, scurvy) at the IBD visit when plasma vitamin C level was obtained. These included fatigue, arthritis/arthralgias, skin findings (rash, hyperpigmentation, *etc.*), easy bruising, gingivitis, poor wound healing, perifollicular findings (hemorrhage, folliculitis) and alopecia.

Outcomes and definitions

The primary study outcome was the prevalence of vitamin C deficiency in IBD patients. Vitamin C deficiency was defined as plasma vitamin C level < 11.4 μmol/L[24,25]. Inadequate vitamin C level or marginal deficiency was defined as 11.4-28.0 μmol/L, consistent with prior studies[24,25]. Secondary analyses were performed to assess whether clinical, biomarker or endoscopic disease activity were associated with deficiency. Patients were assessed for clinical disease activity using the Harvey-Bradshaw Index for CD[26] and modified partial Mayo score for UC[27]. Clinically active disease was defined as Harvey-Bradshaw Index > 5 for CD. For UC, clinically active disease was defined as either stool frequency or rectal bleeding > 1 on the modified partial Mayo score. Elevated CRP was defined as > 0.9 mg/dL and elevated fecal calprotectin was defined as > 250 μg/g. Endoscopically severe disease was defined as simple endoscopic score CD > 15 for CD and Mayo endoscopic score ≥ 2 for UC[28-30]. Additional outcomes based on biologic plausibility included the association of vitamin C deficiency with IBD type (CD or UC), obesity (BMI ≥ 30), use of biologic medications, disease location in the small intestine, penetrating disease, IBD-related surgery, elevated CRP, elevated fecal calprotectin, iron deficiency, clinically active disease and endoscopically severe disease.

Statistical analysis

The primary outcome described the prevalence of vitamin C deficiency in patients with IBD. To address this outcome, based on previous data in 137 CD patients showing a 15% prevalence of vitamin C deficiency[17], in our exploratory cohort of 301 patients, we expected that a two-sided 95% confidence interval (CI) for the prevalence could be constructed to be within ± 4.0% of the observed prevalence

proportion. Statistical review was performed by the corresponding author, who has extensive experience performing statistical analyses for clinical research.

For secondary outcomes, variables (listed above) were selected based on biologic plausibility for abnormal vitamin C absorption. To address these secondary outcomes, we performed chi-squared tests or Fisher's exact tests as appropriate to compare the proportions of vitamin C deficiency between groups. A multivariate logistic regression was performed on covariates selected based on biologic plausibility. These included presence of small bowel disease, penetrating disease, history of IBD-related surgery, obesity, current biologic medication use, elevated CRP, and clinically active disease. Variables with $P \leq 0.2$ were selected for inclusion in the final model. CRP was selected as the sole objective inflammatory marker for sample size considerations (*i.e.*, fecal calprotectin and endoscopy data had limited sample size) and to avoid multicollinearity with these other inflammatory assessments. All analyses were performed using Stata Version 16.0 (StataCorp, College Station, TX). Continuous variables were expressed as means ± SD. The multivariate analysis was expressed as odds ratio (OR) with 95%CI.

RESULTS

Baseline demographics

A total of 301 CD or UC patients with available plasma vitamin C levels were included in the study. Baseline characteristics of the entire cohort are described in Table 1. The mean age of the cohort was 47.6 ± 17.4 years. One hundred ninety (63.1%) subjects were female, and 230 (76.4%) were Caucasian. A total of 201 (66.8%) patients had a diagnosis of CD and 100 (33.2%) had a diagnosis of UC. The mean duration of disease was 17.0 ± 13.6 years. A total of 109 (36.2%) patients had a history of IBD-related surgery and 133 patients (44.2%) were undergoing treatment with a biologic agent at the time of plasma vitamin C level collection. Six patients (2.0%) were active smokers and 42/291 (14.4%) had a BMI ≥ 30. Fifty-nine of 252 patients (23.4%) had iron deficiency, 1/264 (0.4%) had vitamin B12 deficiency, and 38/259 (14.7%) had vitamin D deficiency or insufficiency. Of 292 patients with available disease activity scores, 134 (45.9%) had clinically active disease. Of 113 patients with available endoscopies, 20 (17.7%) had endoscopically severe disease.

Proportion of IBD patients with vitamin C deficiency

The mean vitamin C level was 35.7 ± 27.8 μmol/L in the entire IBD cohort. For analysis of the primary outcome, 21.6% of IBD patients (65/301) had vitamin C deficiency (< 11.4 μmol/L). An additional 24.6% of IBD patients (74/301) had inadequate vitamin C levels (11.4-28.0 μmol/L). CD patients had numerically higher prevalence of vitamin C deficiency than those with UC, although this result did not reach statistical significance (24.4% *vs* 16.0%, $P = 0.1$, Figure 1).

Secondary outcomes: Factors associated with vitamin C deficiency in all IBD patients

In all IBD patients, those with elevated CRP had higher proportions of vitamin C deficiency (39.1% *vs* 16.9%, $P < 0.001$, Table 2) compared to those without elevated CRP. Similarly, patients with elevated fecal calprotectin had higher rates of vitamin C deficiency (50.0% *vs* 20.0%, $P = 0.009$) compared to those without fecal calprotectin elevation. In a subgroup with available endoscopic data, those with severe inflammation ($n = 20$) had numerically higher deficiency rates compared to those without severe inflammation (35.0% *vs* 22.6% $P = 0.2$). However, comparable rates of deficiency existed between those with and without clinically active disease (26.1% *vs* 18.4%, $P = 0.1$). Obesity (35.7% *vs* 19.7%, $P = 0.02$) and current biologic medication use (28.6% *vs* 15.6%, $P = 0.006$) were associated with increased rates of vitamin C deficiency on univariate analysis. Among patients on current biologic therapy ($n = 133$), there were higher proportions of vitamin C deficiency in those using TNF-α inhibitors (17/48) compared with those using non-TNF-α (16/85) biologics (35.4% *vs* 18.8%, $P = 0.03$). Iron deficiency (28.8% *vs* 20.2%, $P = 0.2$), vitamin D deficiency/insufficiency (28.9% *vs* 21.3%, $P = 0.3$), surgery (25.7% *vs* 19.3%, $P = 0.2$), and active smoking (50.0% *vs* 21.0%, $P = 0.1$) were not associated with higher deficiency rates. On multivariate analysis, elevated CRP was the only factor significantly associated with vitamin C deficiency (OR = 3.1, 95%CI: 1.5-6.6, $P = 0.003$). Presence of small bowel disease, penetrating disease, history of IBD-related surgery, obesity, use of a biologic agent, and clinically active disease were not.

Secondary outcomes: Factors associated with vitamin C deficiency stratified by disease

Among CD patients, patients with penetrating disease had significantly higher rates of vitamin C deficiency compared to patients without penetrating disease (36.2% *vs* 20.8%, $P = 0.03$, Table 2). In CD patients, both elevated CRP (41.2% *vs* 17.9%, $P = 0.001$) and fecal calprotectin (56.3% *vs* 26.3%, $P = 0.04$) were persistently associated with higher proportions of vitamin C deficiency compared to those without elevated biomarkers. In subgroups of CD patients with endoscopic data available, those with endoscopically severe disease ($n = 12$) had numerically increased prevalence of vitamin C deficiency (41.7% *vs* 27.7%, $P = 0.3$). Similarly, CD patients with clinically active disease had numerically higher rates of deficiency (30.2% *vs* 20.2%, $P = 0.1$). CD patients with small bowel involvement did not have higher

Table 1 Baseline characteristics

	All IBD patients (*n* = 301)
Female sex	190 (63.1%)
Age (yr)	47.6 ± 17.4
Ethnicity	
Caucasian	230 (76.4%)
Hispanic	16 (5.3%)
African-American	5 (1.7%)
Asian	14 (4.7%)
Not specified	36 (12.0%)
BMI	24.8 ± 5.2
Obesity (BMI ≥ 30)[1]	42 (14.4%)
Active smoking	6 (2.0%)
CD	201 (66.8%)
Disease location	
Ileal	57 (28.4%)
Colonic	34 (16.9%)
Ileocolonic	108 (53.7%)
Upper disease	10 (5.0%)
Behavior	
Non-stricturing, non-penetrating	106 (52.7%)
Stricturing	74 (36.8%)
Penetrating	47 (23.4%)
UC	100 (36.8%)
Disease location[1]	
Proctitis	14 (14.7%)
Left-sided colitis	45 (47.4%)
Pancolitis	36 (37.9%)
Disease duration (yr)	17.0 ± 13.6
IBD related surgery	109 (36.2%)
IBD medications	
Current biologic use	133 (44.2%)
Past/ever biologic use	166 (55.1%)
Clinically active disease[1]	134 (45.9%)
CD	96 (49.2%)
UC	38 (39.2%)
Endoscopically severe disease[1]	20 (17.7%)
CD	12 (15.6%)
UC	8 (22.2%)

[1]Ten patients had unknown body mass index. Five ulcerative colitis (UC) patients had unknown disease location. Nine patients did not have disease activity available (6 Crohn's disease, 3 UC). One hundred thirteen inflammatory bowel disease patients had endoscopies available.
Clinically active disease was defined as Harvey-Bradshaw index > 5 for Crohn's disease (CD), and stool frequency or rectal bleeding > 1 on modified partial Mayo score for ulcerative colitis (UC). Endoscopically severe disease was defined as simple endoscopic score CD > 15 in CD and endoscopic Mayo

score ≥ 2 in UC. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; BMI: Body mass index.

Table 2 Prevalence of vitamin C deficiency in covariate populations

Covariates	Prevalence of vitamin C deficiency in patients with covariate	Prevalence of vitamin C deficiency in patients without covariate	*P* value
IBD type			
CD	49/201 (24.4%)	-	0.1
UC	16/100 (16.0%)	-	0.1
Small bowel disease	38/165 (23.0%)	11/36 (30.6%)	0.3
Penetrating disease	17/47 (36.2%)	32/154 (20.8%)	0.03[1]
IBD related surgery	28/109 (25.7%)	37/192 (19.3%)	0.2
CD	25/96 (26.0%)	24/105 (22.9%)	0.6
UC	3/13 (23.1%)	13/87 (14.9%)	0.4
Obesity (BMI ≥ 30)	15/42 (35.7%)	49/249 (19.7%)	0.02[1]
Active smoking	3/6 (50.0%)	62/295 (21.0%)	0.1
Current biologic use	38/133 (28.6%)	26/167 (15.6%)	0.006[1]
CRP > 0.9 mg/dL	25/64 (39.1%)	36/213 (16.9%)	< 0.001[1]
CD	21/51 (41.2%)	24/134 (17.9%)	0.001[1]
UC	4/13 (30.8%)	12/79 (15.2%)	0.2
Fecal calprotectin > 250 ug/g	10/20 (50.0%)	12/60 (20.0%)	0.009[1]
CD	9/16 (56.3%)	10/38 (26.3%)	0.04[1]
UC	1/4 (25.0%)	2/22 (9.1%)	0.4
Iron deficiency	17/59 (28.8%)	39/193 (20.2%)	0.2
Vitamin D deficiency/insufficiency	11/38 (28.9%)	47/221 (21.3%)	0.3
Clinically active disease	35/134 (26.1%)	29/158 (18.4%)	0.1
CD	29/96 (30.2%)	20/99 (20.2%)	0.1
UC	6/38 (15.8%)	9/59 (15.3%)	0.9
Endoscopically severe disease	7/20 (35.0%)	21/93 (22.6%)	0.2
CD	5/12 (41.7%)	18/65 (27.7%)	0.3
UC	2/8 (25.0%)	3/28 (10.7%)	0.3

[1]Patients with penetrating disease, obesity, biologic use, elevated C-reactive protein and elevated fecal calprotectin had increased frequency of vitamin C deficiency.

Clinically active disease was defined as Harvey-Bradshaw index > 5 for Crohn's disease (CD), and stool frequency or rectal bleeding > 1 on modified partial Mayo score for ulcerative colitis (UC). Endoscopically severe disease was defined as simple endoscopic score CD > 15 in CD and endoscopic Mayo score ≥ 2 in UC. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; BMI: Body mass index; CRP: C-reactive protein.

rates of vitamin C deficiency compared to those without small bowel involvement (23.0% *vs* 30.6%, P = 0.3).

In small subgroups of UC patients with available data, numerical differences persisted between those with elevated CRP (n = 13) and those with elevated fecal calprotectin (n = 4) when compared to those without elevated biomarkers (CRP: 30.8% *vs* 15.2%, P = 0.2; fecal calprotectin: 25.0% *vs* 9.1%, P = 0.4). In a small subset of UC patients with available endoscopic data, those with endoscopically severe disease (n = 8) had numerically increased frequency of vitamin C deficiency (25.0% *vs* 10.7%, P = 0.3). However, clinically active disease was not associated with higher rates of vitamin C deficiency when compared to those with quiescent disease (15.8% *vs* 15.3%, P = 0.9).

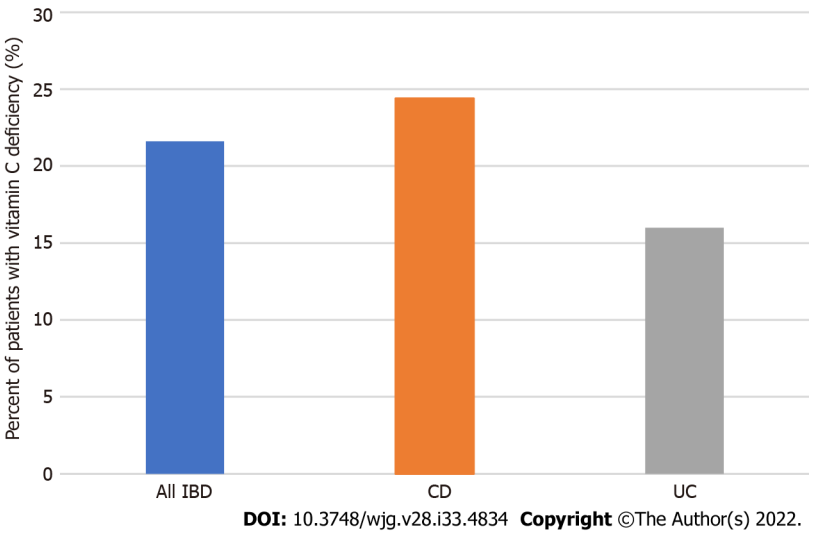

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Figure 1 Prevalence of vitamin C deficiency in inflammatory bowel disease. In total, 21.6% of all inflammatory bowel disease patients had vitamin C deficiency, including 24.4% of Crohn's disease patients and 16.0% of ulcerative colitis patients. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis.

Symptoms of vitamin C deficiency

When comparing patients with and without vitamin C deficiency, there was no difference in the presence of one or more clinical features of scurvy (66.2% *vs* 58.5%, $P = 0.3$, Table 3). Furthermore, both groups had similar rates of arthritis, cutaneous findings, easy bruising, gingivitis, perifollicular findings and alopecia. Patients with vitamin C deficiency were more likely to report fatigue than those with normal vitamin C levels (43.1% *vs* 27.5%, $P = 0.02$). Moreover, vitamin C deficient patients were more likely to report poor wound healing (4.6% *vs* 0.4%, $P = 0.03$).

DISCUSSION

Though many consider scurvy a historical disease of seafarers, the current study demonstrates that vitamin C deficiency affects a significant minority of IBD patients. In 301 patients, 21.6% of IBD patients had vitamin C deficiency, including 24.4% of CD patients and 16.0% of UC patients. This is approximately three-fold higher than the prevalence of vitamin C deficiency in the overall United States population[8].

Strikingly, in IBD patients with elevated objective markers of inflammation, such as CRP and fecal calprotectin, vitamin C deficiency rates ranged from 39%-50%. Similarly, CD patients with penetrating phenotype had higher deficiency rates. On multivariate analysis, the association between elevated CRP and vitamin C deficiency persisted. To our knowledge, this study uniquely examines the relationship between objectively quantified intestinal inflammation (using endoscopy, $n = 113$, or fecal calprotectin, $n = 80$) and vitamin C deficiency in a large cohort. Subgroup analysis in patients with available endoscopic data was concordant with biomarker data, with numerically higher rates of deficiency in those with significant intestinal inflammation. In UC, biomarkers and endoscopic data were more limited, with few patients in groups with elevated CRP, fecal calprotectin and endoscopic inflammation available. Absolute rates of deficiency were non-significantly lower in UC, but numerical differences between UC patients with and without inflammation were similar to these differences in CD. Notably, even in patients without objective evidence of inflammatory disease - based on CRP, calprotectin, and endoscopic score - rates of deficiency ranged from 17%-23%.

This study is the largest to date to report on the prevalence of vitamin C deficiency in IBD. Additionally, the current study significantly increases available data in both CD and UC by utilizing a well characterized cohort to provide analyses on factors associated with deficiency. Previous smaller studies have shown vitamin C deficiency rates of 15%-84% in CD patients[9,17-20]. The variability of decreased vitamin C levels in these studies largely stems from differences in sample sizes and reference ranges.

While previous studies report inadequate vitamin C intake in UC[31], to our knowledge, there are no prior studies describing proportions with vitamin C deficiency in UC. Vitamin C deficiency would be biologically plausible in CD as CD often affects the primary sites of vitamin C absorption in the small bowel. Interestingly, in UC patients (without small bowel disease), 16% had vitamin C deficiency. While dietary data was not available in this study, avoidance of vitamin C rich foods likely contributed to the development of vitamin C deficiency in patients with UC, as has been reported in previous studies[31]. Moreover, patients with UC often have elevated TNF-α, which has been shown to downregulate

Table 3 Clinical features of vitamin C deficiency

	Vitamin C deficiency (*n* = 65)	Normal vitamin C level (*n* = 236)	*P* value
Presence of ≥ 1 clinical feature(s) of scurvy	43 (66.2%)	138 (58.5%)	0.3
None	22 (33.8%)	98 (41.5%)	-
Fatigue	28 (43.1%)	65 (27.5%)	0.02[1]
Arthritis/arthralgias	27 (41.5%)	96 (40.7%)	0.9
Skin findings (rash, hyperpigmentation)	9 (13.8%)	29 (12.3%)	0.7
Easy bruising	6 (9.2%)	9 (3.8%)	0.1
Gingivitis	3 (4.6%)	6 (2.5%)	0.4
Poor wound healing	3 (4.6%)	1 (0.4%)	0.03[1]
Perifollicular findings (hemorrhage, folliculitis)	2 (3.1%)	1 (0.4%)	0.1
Alopecia	1 (1.5%)	5 (2.1%)	1.0

[1]Patients with vitamin C deficiency were more likely to report fatigue and poor wound healing.
There was no difference in presence of clinical features of scurvy between patients with vitamin C deficiency and those without.

transporters involved in vitamin C uptake[13,14].

The current study found penetrating disease to be associated with vitamin C deficiency. Previously, development of metabolic bone disease has been associated with a penetrating phenotype[32], although few studies have commented on the development of micronutrient deficiency in CD patients with penetrating disease. Penetrating disease often involves the small bowel and also likely reflects more active, refractory CD. Thus, patients with penetrating phenotypes may be at higher risk of both malabsorption - *via* inflamed tissue and enteric fistulas - and poor consumption - *via* dietary avoidance of foods rich in vitamin C that may exacerbate symptoms. These data are consistent with CRP and fecal calprotectin elevations also being associated with deficiency. Interestingly, presence of small bowel disease was not associated with increased risk of vitamin C deficiency in CD, despite the jejunum and ileum being the primary sites of vitamin C absorption. However, historical disease location may have been confounded by patients with inactive small bowel disease. Further studies on patients with active small intestinal disease would be required prior to concluding a lack of association between disease location and deficiency status.

While obesity and biologic medication use have biologic plausibility for deficiency and were associated on univariate analysis[8,13,14,33], the study results in aggregate more strongly support active IBD being associated with vitamin C deficiency. Only CRP was associated with vitamin C deficiency on multivariate analysis. However, it should be noted that in non-IBD populations[8], obesity has been shown to be associated with higher rates of vitamin C deficiency. Prior studies suggest that increased access to low-cost, high-calorie, micronutrient-poor food may explain the association between obesity and multiple vitamin deficiencies[33]. The association of current biologic medication use and vitamin C deficiency is less clear and may be due to this being a marker of a more severe disease course. In a subgroup analysis of patients using biologic therapy, patients on TNF-α inhibitors had higher rates of deficiency compared to those on non-TNF-α agents (*i.e.*, vedolizumab, ustekinumab, *etc.*), which runs counter to our understanding of TNF-α in vitamin C deficiency. TNF-α is known to downregulate transcription of transporters required for vitamin C uptake[13,14], and thus, one might expect that patients using TNF-α inhibitors would have lower, not higher proportions of deficiency. This further supports the use of anti-TNF agents or biologics as a surrogate for disease severity. Future studies may be warranted to better investigate this mechanism.

This study also highlights the difficulty in making a diagnosis of vitamin C deficiency in patients with IBD. In our cohort, there was no difference in the presence of clinical features of scurvy in patients with vitamin C deficiency compared to those with normal vitamin C levels. Many sequelae of vitamin C deficiency are nonspecific and can mimic or coexist with active IBD, including fatigue, arthralgias, oral lesions, bleeding, poor wound healing, anemia, and iron deficiency[15]. Unfortunately, more specific findings in scurvy, such as perifollicular hemorrhage and follicular hyperkeratosis, occur in only a small minority of vitamin C deficient patients, as our study reiterates. Given the challenge of diagnosing scurvy in this population, providers should have a low threshold to test for vitamin C deficiency and counsel on adequate vitamin C intake. Unlike the relapsing and often refractory nature of IBD in many patients, vitamin C supplementation can lead to rapid resolution of symptoms, including some incorrectly ascribed to IBD. Even in IBD patients with unmeasured vitamin C levels, empiric supplementation is not unreasonable, given vitamin C's role as an antioxidant, preventing free radical damage and reducing extracellular oxidants[24]. However, future studies demonstrating that vitamin C supple-

mentation can decrease inflammatory burden or improve clinical symptoms would be necessary prior to recommending empiric supplementation as standard of care for this population.

Study limitations include the use of retrospective chart review. This study did not find an association between clinical disease severity and vitamin C deficiency. However, clinical disease indices, particularly in CD, poorly correlate with mucosal disease[34]. Though this study examined the relationship between endoscopic activity and vitamin C deficiency, analyses on this relationship were limited by the small number of patients with significant endoscopic inflammation (n = 20). Yet, numerical differences based on endoscopic inflammation were consistent with CRP and fecal calprotectin data, suggesting that intestinal inflammation impacts vitamin C deficiency. Multivariate analyses utilized a single objective marker of inflammation to avoid multicollinearity. CRP was selected as few patients had elevated fecal calprotectin (n = 20) or significant endoscopic inflammation (n = 20), whereas 277 patients had CRP data available. Additionally, given the retrospective nature of our study, data are restricted to patients who had plasma vitamin C measurements available; these patients were not necessarily being screened for deficiency. Selection bias may exist as such laboratory values may have restricted the population to those more prone to have vitamin C deficiency. Nonetheless, nearly 40% of our study population had no symptoms of scurvy when their vitamin C level was obtained, indicating a sizable component of our cohort were simply being monitored for standard nutritional deficiencies. An additional limitation of this study was that measurements of all micronutrients were not performed. The retrospective nature of our study also limits our examination of whether inadequate consumption was associated with higher rates of deficiency, or whether fasting status at serum collection impacted vitamin C level, as dietary data was not available. The use of chart review to assess for symptoms of vitamin C deficiency is also a limitation that may have led to under-detection of symptoms related to deficiency. Some providers may not routinely screen for symptoms related to scurvy (*i.e.*, gingivitis, alopecia, *etc.*) and these items may not be reflected in providers' notes. Thus, reporting bias may exist. Despite this, vitamin C deficiency symptoms were infrequently documented. Lastly, this cohort was comprised of patients at an IBD center affiliated with a tertiary care center. Thus, the subjects in this study may have more severe disease, potentially impacting the generalizability of these data.

CONCLUSION

The current study demonstrates that vitamin C deficiency exists in a significant portion of patients with IBD, particularly those with objective markers of active luminal or penetrating disease. Clinical features of scurvy did not differ between patients with and without deficiency, reinforcing the challenge of diagnosing scurvy in this population, as symptoms of vitamin C deficiency and IBD may overlap. In summary, vitamin C deficiency exists in a considerable fraction of IBD patients. Thus, identifying and treating this easily reversible condition in these patients is essential.

ARTICLE HIGHLIGHTS

Research background

Patients with inflammatory bowel disease (IBD) are prone to several nutritional deficiencies, including iron, vitamin B12 and vitamin D. However, there is a lack of data on vitamin C deficiency in this population, as well as the impact of clinical, biomarker and endoscopic disease severity on the development of vitamin C deficiency.

Research motivation

As IBD patients are already at risk of malnutrition and as vitamin C deficiency is an easily reversible condition, it would be valuable to understand the prevalence of and factors associated with vitamin C deficiency in this population.

Research objectives

The primary objective assessed the prevalence of vitamin C deficiency in IBD patients. Secondary objectives evaluated proportions with deficiency between active and inactive IBD - using clinical, laboratory and endoscopic data - to better identify those at risk of deficiency.

Research methods

In this retrospective study, clinical, laboratory and endoscopic data were collected from all Crohn's disease (CD) and ulcerative colitis (UC) patients who had available plasma vitamin C levels presenting to the IBD clinic at a single tertiary care center from 2014 to 2019. Of 353 subjects who met initial search criteria using a cohort discovery tool, 301 ultimately met criteria for inclusion in the study. The primary aim described vitamin C deficiency (≤ 11.4 μmol/L) rates in IBD, with secondary analyses comparing

proportions with deficiency between active and inactive IBD. Multivariate logistic regression analysis evaluated factors associated with deficiency.

Research results

In 301 IBD patients, 21.6% had vitamin C deficiency, including 24.4% of CD and 16.0% of UC patients. Patients with elevated C-reactive protein (CRP) (39.1% *vs* 16.9%, $P < 0.001$) and fecal calprotectin (50.0% *vs* 20.0%, $P = 0.009$) had higher proportions of deficiency compared to those without. Other factors associated with vitamin C deficiency included the presence of penetrating disease ($P = 0.03$), obesity ($P = 0.02$) and current biologic medication use ($P = 0.006$). On multivariable analysis, the objective inflammatory marker utilized for analysis (CRP) was the only factor associated with deficiency (odds ratio = 3.1, 95% confidence interval: 1.5-6.6, $P = 0.003$).

Research conclusions

This study provides the largest data on vitamin C deficiency in patients with IBD, uniquely assesses factors associated with deficiency and provides rigorous assessment of inflammatory status using objective markers. Vitamin C deficiency was common in IBD, particularly those with objective markers of active luminal or penetrating disease. As vitamin C deficiency exists in over one-fifth of IBD patients, it is essential to identify and treat this easily reversible condition in this population.

Research perspectives

Future prospective studies with well characterized cohorts, and data on diet, other micronutrient deficiencies, endoscopic assessment, and vitamin C supplementation, may be warranted to further elucidate factors associated with vitamin C deficiency and the impact of supplementation on clinical course in IBD patients.

FOOTNOTES

Author contributions: Battat R is the guarantor of the article; Gordon BL, Galati JS, Longman RS, Lukin D, Scherl EJ and Battat R contributed to the design of the study; Gordon BL, Galati JS, and Yang S collected the data; Gordon BL and Battat R analyzed the data; Gordon BL, Scherl EJ, Lukin D and Battat R wrote the paper; and all authors read and approved the final version of the manuscript.

Institutional review board statement: This study was reviewed and approved by the institutional review board at Weill Cornell Medicine.

Informed consent statement: This study was conducted retrospectively from data obtained for clinical purposes. The study was approved by the institutional review board at Weill Cornell Medicine, who confirmed that no ethical approval or informed consent was required.

Conflict-of-interest statement: Gordon BL, Galati JS, Yang S have none to report; Longman RS consulted Pfizer, Bristol Myers Squibb; Lukin D consults for Boehringer Ingelheim, Palatin Technologies, Pfizer; research support: AbbVie, Janssen, Kenneth Rainin Foundation, Takeda; Scherl EJ consulted AbbVie, Crohn's and Colitis Foundation of America (CCFA), Entera Health, Evidera, GI Health Foundation, Janssen, Protagonist, Seres, Takeda, Bristol Myers Squibb; research support: AbbVie, AstraZeneca, CCFA, Janssen, Pfizer, National Institute of Health, New York Crohn's Foundation, UCSF-CCFA Clinical Research Alliance, Genentech, Seres, Celgene, UCB, Johns Hopkins University, National Institute of Diabetes and Digestive and Kidney; Shareholder: Gilead; Honoraria: GI Health Foundation, Janssen; Battat R provide research support, fund for the Future Award and Jill Roberts Funds at the Department of Medicine, Weill Cornell Medicine.

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