Micronutrient deficiencies in inflammatory bowel disease: an incidence analysis

Amir Y. Kamel[a], Zachary D. Johnson[a], Isabela Hernandez[b], Christine Nguyen[a], Melanie Rolfe[c], Tiffany Joseph[d], Devika Dixit[e], Steve Shen[e], Naueen Chaudhry[b], Angela Pham[b], S. Devi Rampertab[b] and Ellen Zimmermann[b]

Background Micronutrient deficiencies associated with malnutrition in patients with inflammatory bowel disease (IBD) can lead to complications including anemia, coagulopathy, poor wound healing, and colorectal cancer. This study aimed to investigate micronutrient deficiencies (copper, vitamins A, B_9, E, and K) in IBD patients and highlight associated symptoms to aid in the recognition of micronutrient deficiencies.

Methods A retrospective electronic chart review was performed on adults diagnosed with Crohn's disease or ulcerative colitis hospitalized at a tertiary care center for IBD flare between January 2013 and June 2017. Patients with serum or whole blood micronutrient levels were included. Pregnant and incarcerated patients were excluded.

Results A total of 611 IBD patients (440 Crohn's disease, 171 ulcerative colitis) met the inclusion criteria. Micronutrients were assessed in a subset of IBD patients (copper: 12.3%, A: 10.1%, B_9 : 95.9%, E: 10.3%, and K: 4.6%). Overall, 10.1% of patients had micronutrient deficiencies. The proportion of patients with copper, A, B_9, E, and K deficiencies were 25.4, 53.3, 1.9, 23.7, and 29.4% for Crohn's disease and 50, 52.9, 1.2, 43.8, and 18.2% for ulcerative colitis, respectively. The most common symptoms or historical features associated with micronutrient deficiency were anemia (copper, B_9), muscle weakness (copper, E) thrombocytopenia, fatigue (copper, B_9), diarrhea (B_9), dry skin, hyperkeratosis, pruritus, significant weight loss, elevated C-reactive protein (A), bleeding, and osteoporosis (K).

Conclusion Micronutrient deficiencies are common in IBD patients, yet they are not routinely assessed. Copper, vitamins A, E, and K deficiencies are particularly underrecognized. Associated historical features should raise suspicion and prompt assessment and treatment. Eur J Gastroenterol Hepatol 36: 1186–1192

Introduction

Prevalence of malnutrition in patients with inflammatory bowel disease (IBD) has been reported to range from 20 to 85%, with one study showing rates as high as 60% for Crohn's disease and 56% for ulcerative colitis, respectively [1–3]. Malnutrition is defined by the American Society for Parenteral and Enteral Nutrition (ASPEN) as 'an acute, subacute, or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition with or without inflammatory activity has led to a change in body composition and diminished function' [4]. Malnutrition is perpetuated by the underlying inflammation of IBD and is a direct result of reduced intake, compromised absorption, and increased gastrointestinal losses, subsequently leading to weight reduction and increases in morbidity and mortality. Micronutrients, such as copper, and vitamins E, A, and K, serve important cellular and biological functions. Their deficiencies manifest after prolonged periods of malnutrition due to stress, gastrointestinal loss, starvation, or slow but chronic inadequate intake or compromised absorption [5–7]. Additional factors attributed to Crohn's disease and ulcerative colitis that can contribute to micronutrient deficiencies include a persistent hypermetabolic state, IBD medication side effects, and long-term parenteral nutrition without adequate supplementation [8]. While protein and energy deficiencies have also been reported, micronutrient deficiencies are likely more common among adults with IBD [9]. Such deficiencies, however, are underrecognized and underreported.

Micronutrient deficiencies can ultimately lead to a myriad of other complications including anemia, poor wound healing, osteoporosis, thrombophilia, and colorectal cancer [1]. In addition, malnourished IBD patients may be more likely to have prolonged hospitalization and higher mortality than IBD patients without nutrient deficiencies [10]. The incidence of these micronutrient deficiencies in hospitalized IBD patients is not well defined based on the currently available literature. Therefore, a comprehensive study is needed to further define the incidence in this population. This study aimed to investigate the incidence of micronutrient deficiencies (copper, vitamins A, B_9, E, and

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[a]Department of Pharmacy, UF Health Shands Hospital, [b]Department of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, University of Florida, Gainesville, [c]Department of Pharmacy Services, Lee Health, Fort Myers, [d]Department of Pharmacy, Orlando Health Orlando Regional Medical Center, Orlando and [e]Department of Internal Medicine, University of Florida, Gainesville, Florida, USA

Correspondence to Amir Y. Kamel, PharmD, BCNSP, FASPEN, Department of Pharmacy, UF Health Shands Hospital, 1600 SW Archer Road, Gainesville, FL 32608, USA

Tel: +1 352 258 2168; e-mail: kamela@shands.ufl.edu

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K) in hospitalized IBD patients and highlight symptoms or historical features to aid in the recognition of the clinical manifestations of micronutrient deficiencies. A concurrent study investigating an additional four other micronutrients (vitamins B_1, B_6, B_{12}, and zinc) is reported separately.

Copper plays an important role in energy generation, and acts as a catalyst for enzyme, protein, and neurotransmitter synthesis [11,12]. It is a micronutrient involved in inflammatory signaling pathways and is primarily absorbed in the duodenum [8]. Patients exhibiting diarrhea as a result of a variety of diseases are at risk for copper deficiency [13]. A copper deficiency could impede its essential functions acting as a cofactor for enzymes and electron transport proteins required for antioxidants, neurotransmitters, histamine metabolism, oxidative phosphorylation, and iron transport [14].

Vitamin A (retinol) is a fat-soluble vitamin, primarily absorbed in the ileum, that aids in defense against infectious pathogens and is critical for vision, cell growth, and wound healing [8]. Steroids, commonly used in the IBD patient population, can decrease absorption of vitamin A. Oral retinal was seen to be an applicable repletion method for vitamin A deficiency in patients displaying fistulas or those in a preoperative period [8]. Oral vitamin A was shown to improve mucosal healing in patients with ulcerative colitis, however, the limitations of the data hinder it from generalizing to a larger population [15].

Vitamins E and K are fat-soluble vitamins. Vitamin E plays a protective role against lipid peroxidation by acting as an antioxidant. It has been shown to have both anti-inflammatory and antioxidative activity and may present a novel therapy for mild to moderate ulcerative colitis [16]. Vitamin K is absorbed in the ileum and It acts as an essential cofactor for the formation of vitamin K-dependent proteins involved in blood coagulation, bone metabolism, inhibition of vascular mineralization, and regulation of other cellular functions [8,17].

Vitamin B_9, or folic acid, is a water-soluble vitamin that is essential in erythropoiesis, nucleic acid synthesis, and the DNA methylation process. Folate absorption occurs in the duodenum and upper jejunum of the small intestine. Folate deficiency can lead to macrocytosis, erythroblast apoptosis, and macrocytic anemia [17,18].

Methods

A single-center retrospective electronic chart review was performed on adults with an *International Classification of Diseases, 9th/10th Revision* (ICD-9/10) code diagnosis of Crohn's disease or ulcerative colitis during their index hospitalization to a tertiary care center for IBD flare between 1 January 2013 and 30 June 2017. Chart review within the EPIC electronic medical record system was completed by multiple reviewers to obtain the patient's age, sex, height, total body weight, ideal body weight, BMI, smoking and alcohol history, and IBD type. Adults (>18 years old) with IBD and reported serum or whole blood micronutrient levels were included. Standard serum or whole blood thresholds for each micronutrient were used. Pregnant and incarcerated patients were excluded.

Serum copper levels were measured with inductively coupled plasma-mass spectrometry, whereas serum vitamins A, E, and K were measured with HPLC-tandem mass spectrometry (ARUP Laboratories, Salt Lake City, Utah, USA). Serum vitamin B_9 levels were measured with DxI immunoassay (UF Health Shands Laboratory, Gainesville, Florida, USA).

Statistical analysis

Statistical software JMP PRO (version 17) (SAS Institute, Cary, North Carolina, USA) was used to analyze the data. Descriptive analyses were applied for demographic variables and medical condition variables. Means, SDs, and ranges were calculated for continuous variables; frequencies and percentages were calculated for categorical variables. The chi-square test or Fisher's exact test was used to calculate statistical differences. Results are reported in number of patients (n), means, and percentages where noted.

Results

During the study period, 814 entries were screened, and 611 unique IBD patients were identified, after removing duplicates, including 440 patients with Crohn's disease and 171 with ulcerative colitis. Among the 611 IBD patients screened, 62 (10.1%) had at least one micronutrient deficiency of interest. Of the 62 patients identified with micronutrient deficits, the mean age was 43 years old and approximately 53% of patients were female. The full demographic characteristics of the study population are listed in Table 1.

Eighteen of 71 Crohn's disease patients (25.4%) and two of four ulcerative colitis patients (50%) who had a reported copper level were shown to have a deficiency. Twenty-four of 45 Crohn's disease patients (53.3%) and nine of 17 ulcerative colitis patients (52.9%) had a vitamin A deficiency. Vitamin B_9 was found to be deficient in 1.9% of Crohn's disease patients and 1.2% of ulcerative colitis patients, respectively, whereas vitamin E was found to be deficient in 23.7% of Crohn's disease patients and 43.8% of ulcerative colitis patients. Vitamin K was deficient in 29.4% of Crohn's disease patients and 18.2% of ulcerative colitis patients (Tables 2 and 3).

Symptoms and clinical characteristics of each micronutrient deficiency, stratified by IBD type, are presented in Table 4. The most common symptoms or historical features associated with micronutrient deficiency were anemia (copper, B_9), muscle weakness (copper, E) thrombocytopenia (copper), fatigue (copper), neurological symptoms, (B_9), vitamin D deficiency (copper), diarrhea (B_9), dry skin, hyperkeratosis, pruritus, anorexia, loss of appetite, elevated C-reactive protein (A), significant weight loss (A), bleeding, and osteoporosis (K).

Montreal classification was used to assess pertinent disease characteristics reported in Table 5 for Crohn's disease patients and Table 6 for ulcerative colitis patients for their respective scoring tools. Statistical differences were found between deficient and nondeficient patients in Montreal L (location of disease) ($P = 0.042$) and Montreal B (disease behavior) ($P < 0.001$). The stratification of these results by micronutrients for Crohn's disease and ulcerative colitis patients is presented in Supplementary Appendix A, Supplemental digital content 1, *http://links.lww.com/EJGH/B51* and Supplementary Appendix B, Supplemental digital content 2, *http://links.lww.com/EJGH/B52*, respectively.

Table 1. Patient demographics

Characteristics	All patients, $N = 611$	Micronutrient deficient patients, $n = 62$	Crohn's disease			Ulcerative colitis		
			All Crohn's disease patients, $n = 440$	Nondeficient, $n = 393$	Deficient, $n = 47$	All ulcerative colitis patients, $n = 171$	Nondeficient, $n = 156$	Deficient, $n = 15$
Age, mean (interquartile range), years	44.8 (18–96)	43.7 (20–78)	43.5 (18–95)	43.8 (18–95)	41.4 (20–78)	48.6 (18–96)	48.3 (18–96)	50.9 (21–75)
Female, *n* (%)	296 (48.4)	33 (53.2)	227 (51.5)	200 (50.9)	27 (57.4)	69 (40.4)	63 (40.4)	6 (40.0)
Weight, mean ± SD, kg	72.5 ± 21.2	66.6 ± 21.4	72.4 ± 21.5	73.5 ± 21.2	64.8 ± 22.0	72.7 ± 20.3	72.8 ± 20.6	72.3 ± 18.8
BMI, mean ± SD, kg/m^2	25.5 ± 7.1	22.9 ± 6.4	25.4 ± 7.2	25.9 ± 7.2	22.0 ± 6.3	25.9 ± 6.8	26.0 ± 6.9	25.3 ± 6.4
Length of stay, mean (interquartile range), days	8.6 (0–96)	16.5 (1–96)	8.3 (0–96)	7.1 (0–70)	15.7 (1–94)	9.2 (0–74)	8.4 (0–69)	19.9 (1–74)
Alcohol use, *n* (%)								
Yes	122 (20)	9 (15)	85 (19)	78 (20)	7 (15)	37 (22)	35 (22)	2 (13)
No	368 (60)	44 (71)	252 (57)	220 (56)	32 (68)	116 (68)	104 (67)	12 (80)
Not asked	121 (20)	9 (15)	103 (23)	95 (24)	8 (17)	18 (11)	17 (11)	1 (7)
Tobacco use, *n* (%)								
Yes/passive	91 (15)	6 (10)	79 (18)	73 (19)	6 (13)	12 (7)	12 (8)	0 (0)
Quit	165 (27)	19 (31)	107 (24)	92 (23)	15 (32)	58 (34)	54 (35)	4 (27)
Never	241 (39)	28 (45)	158 (36)	139 (35)	19 (40)	83 (49)	74 (47)	9 (60)
Not asked	114 (19)	9 (15)	96 (22)	89 (23)	7 (15)	18 (11)	16 (10)	1 (7)

Table 2. Deficiency incidence: Overall incidence of micronutrient deficiency among inflammatory bowel disease patients

Incidence (%)	CD	UC
Cu	25.4%	50.0%
Vitamin A	53.3%	52.9%
Vitamin B_9	1.9%	1.2%
Vitamin E	23.7%	43.8%
Vitamin K	29.4%	18.2%

Incidence was calculated by dividing the number of patients deficient in the given micronutrient by the total number of patients that had laboratory results for the micronutrient.
CD, Crohn's disease; Cu, copper; UC, ulcerative colitis.

Discussion

In this cohort of 611 IBD patients, we collected associated symptoms related to each micronutrient deficiency to highlight the importance of detection and to help guide clinicians in identifying such deficiencies. In one report, the incidence of micronutrient deficiency was found to be more than 50% among IBD patients [10]. Others have reported incidences up to 82.5% in Crohn's disease and 11.3% in ulcerative colitis, respectively [19]. As micronutrients play important roles in inflammatory signaling, antioxidant functions, and cellular machinery processes, it is imperative that deficiencies are able to be identified and corrected among this patient population. The European Society for Clinical Nutrition and Metabolism 2017 guidelines recommend micronutrients to be regularly checked in IBD patients and deficiencies to be adequately corrected [20].

Copper

In our study, the most common symptoms associated with copper deficiency were fatigue (67 and 100%), anemia (61 and 100%), muscle weakness (56 and 100%), and thrombocytopenia (22 and 100%) for Crohn's disease and ulcerative colitis patients, respectively.

Copper deficiency is rare due to its stores in the liver, muscle, and bone. Studies reporting the incidence of copper deficiency among IBD patients are inconsistent. Filippi *et al*. [21] showed a decrease in serum copper levels in Crohn's disease patients in clinical remission compared with controls. Other studies, however, have found that patients with ulcerative colitis displayed similar serum copper levels to controls, with some displaying elevated levels [22,23].

When analyzing systemic inflammation, it is valuable to look at the ratio of copper to zinc compared with the concentration of either element alone. In the presence of systemic inflammation, serum concentrations of zinc decrease while serum copper concentrations increase, creating a higher copper-to-zinc ratio [24]. This is linked to malnutrition, inflammation, active immune response, and increased oxidative stress [25]. In previous studies, a higher copper-to-zinc ratio was seen in patients with active ulcerative colitis compared with controls [23] and both ulcerative colitis and Crohn's disease patients, despite lower disease severity and clinical remission [26]. These findings may contradict the results of our study as we found 25.4% of Crohn's disease and 50% of ulcerative colitis patients to be deficient in copper, although zinc levels were not reported in this study.

This marker requires further assessment among IBD patients to properly be used as an essential marker for inflammation or the need for supplementation. Currently, available recommendations for copper supplementation come from ASPEN Clinical Guidelines, suggesting 0.3–0.5 mg copper per day added to the patient's parenteral nutrition [27] and a dose of 3–8 mg per day of copper as gluconate or sulfate for oral repletion in case of deficiency [28].

Vitamin A

Vitamin A deficiency is typically measured using serum retinol concentrations. Using this as the indicator for deficiency, patients with Crohn's disease and ulcerative colitis were both shown to have lower levels than control populations [29]. A case study showed a correlation between night blindness in a patient with Crohn's

Table 3. Deficiency incidence: Breakdown of patient entries and micronutrient deficiency among inflammatory bowel disease patients

	Cu	Vitamin A	Vitamin B_9	Vitamin E	Vitamin K	Total	Total patients without duplicates
Total unique entries							
CD	71	45	420	47	17	600	440
UC	4	17	166	16	11	214	171
Subtotal	75	62	586	63	28	814	611
Unique deficient							
CD	18	24	8	9	5	64	47
UC	2	9	2	7	2	22	15
Subtotal	20	33	10	16	7	86	62

Reported is the number of patients that were deficient or not deficient in each micronutrient, stratified by inflammatory bowel disease status.
CD, Crohn's disease; Cu, copper; UC, ulcerative colitis.

Table 4. Patient symptoms associated with deficiency

Cu			A		
	CD	UC		CD	UC
Total	18	2	Total	24	9
Cu value, reference range (mcg/dl)	80–155		A value, reference range (mg/L)	0.3–1.2	
Cu value of deficient patients, mean ± SD (mcg/dl)	57.7 ± 16.9	59.0 ± 14.1	A value of deficient patients, mean ± SD (mg/L)	0.18 ± 0.07	0.17 ± 0.08
Cu value of nondeficient patients, mean ± SD (mcg/dl)	116.7 ± 24.2	124 ± 38.2	A value of nondeficient patients, mean ± SD (mg/L)	0.54 ± 0.24	0.47 ± 0.14
Ceruloplasmin deficient	2 (11)	1 (50)	Corneal xerosis	0 (0)	2 (22)
Elevated white blood cell count	2 (11)	0 (0)	Dry skin/hyperkeratosis/ pruritus	16 (67)	8 (89)
Low neutrophils	0 (0)	1 (50)	Anorexia/loss of appetite/ significant weight loss	21 (88)	7 (78)
Anemia	11 (61)	2 (100)	Frequent infections	17 (71)	4 (44)
Neutropenia	1 (6)	1 (50)	Impaired taste	3 (13)	2 (22)
Muscle weakness	10 (56)	2 (100)	Fragile fingernails	3 (13)	0 (0)
Spasticity	0 (0)	0 (0)	Elevated CRP	18 (75)	3 (33)
Neuropathy	2 (11)	0 (0)			
Ataxia	1 (6)	0 (0)	E		
Visual impairment	0 (0)	0 (0)		CD	UC
Thrombocytopenia	4 (22)	2 (100)	Total	9	7
Myelopathy	0 (0)	0 (0)	E value, reference range (mg/L)	5.5–18	
Fatigue	12 (67)	2 (100)	E value of deficient patients, mean ± SD (mg/L)	4.4 ± 1.1	4.2 ± 1.0
Arthritis	3 (17)	0 (0)	E value of nondeficient patients, mean ± SD (mg/L)	11.4 ± 6.8	9.2 ± 2.4
Osteoarthritis	1 (6)	0 (0)	Muscle weakness	5 (56)	4 (57)
Feeling cold	1 (6)	0 (0)	Ataxia	1 (11)	0 (0)
Frequent infections	0 (0)	0 (0)	Retinopathy	0 (0)	0 (0)
Vitamin D deficient	8 (44)	0 (0)	Peripheral neuropathy	0 (0)	1 (14)

B_9			K		
	CD	UC		CD	UC
Total	8	2	Total	5	2
B_9 value, reference range (ng/ml)	>5.5		K value, reference range (nmol/L)	0.22–4.88	
B_9 value of deficient patients, mean ± SD (ng/ml)	3.9 ± 1.0	4.1 ± 0.6	K value of deficient patients, mean ± SD (nmol/L)	0.16 ± 0.04	0.14 ± 0.05
B_9 value of nondeficient patients, mean ± SD (ng/ml)	25.3 ± 91.2	24.8 ± 85.5	K value of nondeficient patients, mean ± SD (nmol/L)	1.91 ± 4.2	0.97 ± 0.50
Megaloblastic anemia	5 (63)	2 (100)	Bleeding	4 (80)	1 (50)
Neurological symptoms	8 (100)	2 (100)	Osteoporosis	3 (60)	1 (50)
Skin pallor, mouth sores	3 (38)	0 (0)	Vascular calcification	1 (20)	1 (50)
Diarrhea	8 (100)	2 (100)	Coronary artery disease	1 (20)	0 (0)
Colorectal/lung cancer	1 (13)	0 (0)			
Alcohol abuse	2 (25)	0 (0)			

Values are represented as *n* (%) unless otherwise noted.
Elevated white blood cell count is defined as >10 × 10^3/μl, low absloute neutrophils defined as <1.7 × 10^3/μl, ceruloplasmin deficient defined as <18 mg/dl, elevated C-reactive protein defined as >5 mg/L, vitamin D deficient defined as <30 ng/ml.
CD, Crohn's disease; CRP, C-reactive protein; Cu, copper; UC, ulcerative colitis.

disease and a serum retinol deficiency, with normal eyesight being restored following vitamin A compensation [30]. For patients with ulcerative colitis, there has been shown to be an increase in vitamin A deficiency from diagnosis to 1-year follow-up, despite a decrease in disease severity, while patients with Crohn's disease saw an

Table 5. Montreal classification of Crohn's disease by micronutrient deficiency status

		Nondeficient, *n* = 393	Deficient, *n* = 47	*P*-value
Montreal A	1	0 (0)	0 (0)	0.767
	2	82 (21)	16 (34)	
	3	59 (15)	13 (28)	
Montreal L	1	46 (12)	11 (23)	**0.042**
	2	47 (12)	3 (6)	
	3	47 (12)	15 (32)	
	4	1 (0.3)	0 (0)	
Montreal B	1	82 (21)	10 (21)	**<0.001**
	2	26 (7)	2 (4)	
	3	33 (8)	15 (32)	
	4	0 (0)	2 (4)	

Values are represented as *n* (%).
Bold indicates the significance of *P* values.
Montreal classification for Crohn's disease patients is represented. Montreal A correlates to age of diagnosis (A1: below 16 years, A2: between 17 and 40 years, A3: above 40 years). Montreal L correlates to the location of disease (L1: ileal, L2: colonic, L3: ileocolonic, L4: isolated upper disease). Montreal B correlates to disease behavior (B1: nonstricturing, nonpenetrating, B2: stricturing, B3: penetrating).

Table 6. Montreal classification of ulcerative colitis by micronutrient deficiency status

		Nondeficient, *n* = 156	Deficient, *n* = 15	*P*-value
Montreal E	1	6 (2)	1 (2)	1.000
	2	13 (3)	2 (4)	
	3	26 (7)	6 (13)	
Montreal S	0	0 (0)	0 (0)	0.910
	1	7 (2)	3 (6)	
	2	3 (1)	2 (4)	
	3	4 (1)	3 (6)	
	4	1 (0.3)	0 (0)	

Values are represented as *n* (%).
Montreal classifications for ulcerative colitis (UC) patients are represented. Montreal E correlates to the extent of disease [E1: ulcerative proctitis, E2: left-sided UC (distal UC), E3: extensive UC (pancolitis)]. Montreal S correlates to the severity of the disease (S0: clinical remission, S1: mild UC, S2: moderate UC, S3: severe UC).

improvement, or decrease, in vitamin A deficiency following a 1-year follow-up [31]. In our study, the most common vitamin A deficiency symptoms we found were anorexia, loss of appetite, significant weight loss (88 and 78%), dry skin, hyperkeratosis, pruritus (67 and 89%), and elevated C-reactive protein (75 and 33%) for both Crohn's disease and ulcerative colitis patients, respectively. As roughly half of our study patients proved to be deficient in vitamin A with associated symptoms of deficiency, this highlights the increasing need for better identification and repletion of vitamin A in deficient patients with IBD.

Since vitamin A is stored in the liver, deficiency diagnosis may be influenced by if these liver reserves have declined [32]. This assessment, in combination with serum retinol, displayed an even higher prevalence of Vitamin A deficiency in patients with Crohn's disease compared with those diagnosed by serum retinol exclusively [33].

Vitamin E

The most common vitamin E deficiency symptoms we found were muscle weakness (56 and 57%) for both Crohn's disease and ulcerative colitis patients, respectively, which correlates with findings from previous observations. Meta-analysis showed lower levels of vitamin E in Crohn's disease patients than controls [33]. Some studies, however, show no correlation between IBD diagnosis and vitamin E deficiency [34]. Vitamin E deficiency may result in increased red cell hemolysis and increased lipid peroxidation and may manifest as muscle weakness and abnormal sensory nerve function [35].

It is unclear how vitamin E should be measured and the clinical impact it should have on these patients. Forms of vitamin E have been shown to have protective effects on intestinal barrier function and the ability to cause positive changes in gut microbiota in mice [36]. When observing the dietary intake of micronutrients, vitamin E was shown to have a high prevalence of inadequate nutrient consumption (63%) [37]. Ingestion of low polyunsaturated fatty acids lowers the requirement of vitamin E since it is absorbed by other fat-soluble vitamins [8].

Vitamin K

The most common vitamin K deficiency symptoms we found were bleeding (80 and 50%), and osteoporosis (60 and 50%) for both Crohn's disease and ulcerative colitis patients, respectively.

An early study showed a connection between vitamin K deficiency in IBD patients [34]. Vitamin K also plays a role in metabolism contributing to osteoblast activity. It was observed that the vitamin K status of Crohn's disease was not only lower than controls but the rate of bone resorption was increased in deficient patients [38]. Although this was shown, supplementation was shown to have no significant effect on bone metabolism [17]. In a meta-analysis comparing control to Crohn's disease patients, vitamin K was significantly lower in Crohn's disease [33]. A case study showed that clinical symptoms that occur due to low levels of vitamin K, ecchymosis, and widespread hematomas, may serve as an initial sign of complex conditions like IBD [39].

Vitamin B_9

The most common vitamin B_9 deficiency symptoms found were neurological symptoms (100 and 100%), diarrhea (100 and 100%), and megaloblastic anemia (63 and 100%) for both Crohn's disease and ulcerative colitis patients, respectively. Those with IBD are at an increased risk of folate deficiency, compared with those in clinical remission and healthy controls, due to impaired nutrient absorption and medications prescribed to patients such as methotrexate and sulfasalazine that lead to excess folate depletion [40]. A meta-analysis confirmed that the average serum folate of IBD patients, specifically those with ulcerative colitis, was significantly lower than controls [41]. While comparing patients with Crohn's disease to those with ulcerative colitis, the prevalence of folate deficiency was found to be 22.2% compared with 4.3% [18].

Although unclear if IBD was the cause of the deficiency, there is a clear link between the deficiency and disease presence. The link between folate deficiency and IBD provides support for the usage of the serum vitamin profile as a complementary biomarker for the assessment of disease

activity [42]. European Crohn's and Colitis Organization (ECCO) recommends annual testing for folate deficiency in all IBD patients or on a case-by-case basis if the patient has either macrocytosis or has stopped using thiopurine [43].

Limitations

Several limitations to this study exist. By design, this is a single-center, retrospective chart review which limits the generalizability to patients outside the study area. In addition, due to the nature of the study, no conclusions can be drawn regarding a cause-and-effect relationship between specific micronutrient deficiency and associated side effects. Associated symptoms were collected with each micronutrient to aid clinicians in identifying symptoms earlier to prevent some of the late irrevocable manifestations as a result of micronutrient deficiency. Micronutrient levels may also be affected in the setting of inflammation, being acute phase reactants, and may have impacted incidence data in our hospitalized study population. Last, the small sample size, especially for ulcerative colitis patients, may limit the interpretation of the results. Particularly, the subpopulations used for reporting Montreal classification were small and had a significant amount of data not able to be obtained. This limits the ability to conclude a correlation between these deficiencies and their disease classification.

Conclusion

Micronutrient deficiencies are common in IBD patients, yet they are not routinely assessed. Copper, vitamin A, E, K, and B_9 deficiencies are particularly underrecognized. Factors contributing to micronutrient deficiencies in IBD patients include reduced absorption, chronic inflammation, reduced intake, drug interactions, and prior surgeries. Associated patient symptoms should raise suspicion and prompt assessment and treatment of micronutrient deficiencies to prevent further sequelae in the IBD patient population.

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Conflicts of interest

There are no conflicts of interest.

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