The Relevance of Vitamin and Iron Deficiency in Patients with Inflammatory Bowel Diseases in Patients of the Swiss IBD Cohort

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Background andAims: Vitamin and iron deficiencies are common in patients with inflammatory bowel disease (IBD) as a result of chronic intestinal inflammation, increase in demand, or dietary restrictions. Here, we assessed the frequency of complications in relation to deficiency of iron, folate acid, and vitamin B12 in patients enrolled in the nationwide Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS).

Methods: A total of 2666 patients were included in the study, 1558 with Crohn's disease (CD) and 1108 with ulcerative colitis (UC).

Results: Iron deficiency anemia was detected in 19.6% of CD patients and 21.6% of UC patients. In CD patients low BMI and nonsmoker status were positively associated with anemia. In both CD and UC, malabsorption syndrome, defined as failure of the GI tract to absorb 1 or more substances from the diet, was found to be significantly associated with anemia (6.2% and 3.8%, respectively) and current steroid use (40% CD, 52.7% UC). In CD patients with ileal (31.7% vs 20%) and colonic (29.9% vs 25%) disease location folate deficiency was significantly higher than in patients with ileocolonic CD or upper GI involvement. In CD patients, vitamin B12 deficiency was associated with the onset of stenosis and intestinal surgery (42.9% vs 32.8% and 46% vs 33% for patients with versus without B12 deficiency).

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Author Contributions

Matiar Madanchi analyzed and interpreted the data and wrote the first draft of the manuscript. Nicolas Fournier performed the statistical analysis; Michael Scharl designed, conceived, and supervised the study. All of the authors were essentially involved in the acquisition, analysis, and interpretation of data and revising the article critically for important intellectual content. All of the authors gave final approval of the version to be submitted. The authors had no writing assistance.

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Conclusion: Our data indicate that due to frequent occurrence of deficiency states, regular monitoring and substitution of vitamins and iron are mandatory and may prevent long-term intestinal and extraintestinal complications in IBD patients.

Key Words: anemia, ferritin, iron deficiency, folate acid, vitamin B12, inflammatory bowel disease, Crohn`s disease, ulcerative colitis, vitamins and trace element

INTRODUCTION

Vitamins act as cofactors and coenzymes and are required intermediaries in physiologic human metabolism. They are micronutrient chemical compounds that, with the exception of cholecalciferol, the human body is not able to synthesize. In addition, some specific vitamins, eg, vitamin D or vitamin A, have been reported to exert anti-inflammatory and/or immunomodulatory effects.[1] In inflammatory bowel disease(IBD) patients, vitamin deficiencies are often due to malnutrition or malabsorption (due to inflamed, malfunctioning mucosa and diarrhea or specific diet changes),[2] which often results in anemia and negatively impacts quality of life.[1, 3–5]

Iron plays an important role in the long-term management of IBD patients. A systematic review reported an overall prevalence of anemia occurring in 24% of IBD patients , in particular 27% in patients with CD and 21% in patients with UC.[6] Iron deficiency and chronic disease are the most important causes of anemia in IBD patients.[7, 8] Other types of anemia, such as vitamin B12 megaloblastic anemia, accounts only for 1.5% of all anemia in IBD patients.[9] However, vitamin B12 and folic acid deficiency are common in IBD patients and supplementation of those vitamins represents best standard of care.[10] Because ileal location of CD or ileocecal resections may lead to vitamin B12 malabsorption, it is anticipated that patients with CD are at greater risk for deficiency.[11–14] Other less frequent causes of vitamin B12 deficiency may be fistulas, small intestinal bacterial overgrowth (SIBO), reduced alimentary intake, increased physiologic requirements, protein losing enteropathy, and hepatic dysfunction.[15, 16] Folate deficiency is common in IBD patients and often linked to sulfasalazine and/or methotrexate (MTX) therapy.[12, 17, 18] Therefore, annually folate level measurement is recommended in these patients.[19]

An important preventive measure in the management of IBD patients is to provide proper nutrition (especially a fiber- rich diet), that may play a role in maintaining remission in those patients.[20] The selection of a proper therapy, such as biological therapy, which is used with increasing frequency, seems not only to mitigate the inflammatory process in the gastrointestinal (GI) tract, but also to provide beneficial effects on the nutritional status of patients with CD, thus denoting the increasing importance of medications in vitamins and micronutrient levels.[21]

Taken together current evidence suggests that vitamins might play an important role for the disease course and outcome of IBD patients. It is of great importance to gain a deeper understanding about vitamin and iron status via regular nutritional monitoring in IBD patients. In this report, using the well-characterized patient collective of the Swiss IBD Cohort Study (SIBDCS), we analyzed the frequency of complications and the association of specific patient characteristics, such as body mass index (BMI) or smoking status, in relation to iron-deficiency anemia and vitamin B12 and folate deficiency. This will help to identify a link between the lack of iron and/or vitamins and possible consequences on disease outcome that might provide the base for an optimized patient care.

METHODS

Patient Data

Data were retrieved from the nationwide SIBDCS. The SIBDCS is a multicenter prospective observational population-based study and includes patients with IBD from Switzerland. The study was extended to all regions of Switzerland in 2006 in a multidisciplinary effort by gastroenterologists, pathologists, psychologists, and bioinformatics specialists. The cohort study is funded by ongoing support of the Swiss National Science Foundation. For inclusion in the SIBDCS, all patients must have a diagnosis established at least 4 months before inclusion. Data are prospectively collected once a year and entered into a central database.[22]

Study Design

Using the exclusive patient collective of the SIBDCS, we evaluated iron, hemoglobin, ferritin, folic acid, and vitamin B12 levels in IBD patients and assessed potential associations with specific diseases characteristics. All patients of the SIBDCS were included in the initial data analysis. Univariate and multivariate logistic regression analyses were performed. We included all patients with CD, UC, and indeterminate colitis (IC) available in the cohort for our study. The following possible explanatory variables were considered. First, epidemiological characteristics were considered: diagnosis of CD, UC, or IC, age; disease duration (years); gender; age at diagnosis; BMI; and smoking status. Patients with CD were considered as a single entity and patients with Crohn's colitis and Crohn's ileitis were not distinguished. Second, disease characteristics were reviewed: activity index; initial and current disease location; extraintestinal manifestations (EIM); existence of stenosis, fistula, fissure, and abscess; and intestinal surgery. Third, selected medications were considered: 5-ASA, VSL#3, E. coli Nissle 1917, antibiotics, steroids, immunomodulators (azathioprine, 6-mercaptopurin), methotrexate, and anti-TNF antibodies. Complications included colorectal cancer (CRC), colonic dysplasia, osteoporosis/osteopenia, deep venous thrombosis, pulmonary embolism, gallstones, nephrolithiasis, massive hemorraghe, perforation/peritonitis, and growth failure.

Malabsorption syndrome, defined as failure of the GI tract to absorb 1 or more substances from the diet, also was determined as a complication. As supplementation therapy, we considered the consumption of magnesium, calcium, folate, iron, lactase, potassium, fish oil, multivitamin preparations, vitamin D**,** vitamin E, vitamin B12, and bioflorin. To assess disease activity and allow comparison between UC (Modified Truelove and Witts activity index, MTWAI) and CD (Crohn's disease activity index, CDAI), disease activity measures were normalized to a value between 0 and 100 and expressed as an activity index. In particular, IBD medication and supplementation therapy was documented by the treating physician in the specific SIBDCS questionnaires at patient inclusion and follow-ups and by the patient questionnaires.

Definitions of Anemia and Vitamin Deficiency

We analyzed the prevalence of vitamin and iron deficiency, the need for supplementation therapy, and the incidence of anemia using the patient collective of the SIBDCS. A total of 2666 patients were included in the study, 1558 CD patients and 1108 UC patients. Vitamin B12 deficiency was defined as a vitamin B12 serum level below 180 ng/l; the cutoff for folate deficiency was defined as a serum level below 4 ng/mL (9.064 nmol/l).

Anemia was defined as hemoglobin concentration (Hb) <= 12g/dl for nonpregnant women and <= 13 g/dl for men according to the World Health Organization definition. Iron-deficiency anemia was defined by a ferritin level < 30 µg/l in patients without clinical, endoscopic, or biochemical evidence of active disease, according to the 2015 European Crohn´s and Colitis Organisation (ECCO) guidelines.[19] Since ferritin measurements are affected by disease activity, which is defined by CDAI for CD patients and Colitis activity index (CAI) for UC patients and C reactive protein (CRP) values, a serum ferritin up to 100 µg/L may still be consistent with iron deficiency.[19] According to the 2015 ECCO guidelines, in the presence of inflammation, the diagnostic criteria for anemia of chronic disease would be a serum ferritin > 100 µg/L and a transferrin saturation (TfS) < 20 %.[19] However, since transferrin saturation is only very incompletely documented in the SIBDCS, we decided to use the following definitions that already have been published using SIBDCS data: ferritin level between 30 and 100 ug/l together with CDAI >= 150 or CAI >= 6 was defined as iron-deficiency anemia in combination with anemia of chronic disease.[23]

Statistical Analysis

All statistical analyses have been carried out using the Stata Software (v. 14.2, StataCorp, College Station, TX, USA). Normal QQ-plots were used to assess gaussianity of continuous data. Gaussian-distributed data were reported as mean, standard deviation, and range, whereas non-Gaussian data were presented as median, interquartile range, and range. Differences in means between 2 independent groups for Gaussian-distributed data were assessed using the Student's *t* test. Differences in distribution locations between 2independent groups for non-Gaussian data were assessed using the Mann-Whitney-Wilcoxon rank sum test. Categorical data were presented as raw frequencies and relative percentages. Differences in distributions for categorical data between 2 or more groups were assessed using the chi-square test, or the Fisher's exact test in case of insufficient sample size. A P value <0.05 was considered for statistical significance. Multiple testing adjustment was done using the Bonferonni's correction.

Ethical Considerations

The SIBDCS has been approved by the respective ethics committees in Switzerland (Ethics Committee of the Canton Zürch: EK-1316). All patients signed an informed consent and confirmed their participation in the cohort study at the time of enrollment and gave informed consent for data collection and analysis for research purposes. The current substudy has been evaluated and approved by the scientific board of SIBDCS.

RESULTS

Folate Deficiency in IBD Patients

Of the total patient collective, folate levels were available from 755 CD and 480 UC/IC patients. There were 695 out of 755 (92 %) CD patients and 454 out of 480 (94.6 %) UC/IC patients who had a folate deficiency according to out definition. No significant difference in BMI was found between patients showing folate deficiency and those with normal folate levels. However, in both groups of IBD, patients with folate deficiency were more often smokers (Table 1, Supplementary Figs. 1– 2).

CD patients with ileal (31.7 % vs 20 %), only colonic (29.9 % vs 25 %), and unknown disease location (2.9 % vs 1.6 %) showed a significantly higher rate of folate deficiency, whereas ileocolonic location or upper GI involvement was not associated with folate deficiency. Interestingly, CD patients without folate deficiency featured significantly more fistula and fistula/abscess-related surgery (11.9 % vs 26.7 %, P = 0.001; 18.9 % vs 30.0 %, P = 0.037) than patients with folate deficiency. UC/IC patients had no significantly higher prevalence of intestinal complications. In particular, CRC , colonic dysplasia, osteoporosis/osteopenia, anemia, deep venous thrombosis, pulmonary embolism, gallstone, nephrolithiasis, malabsorption syndrome, massive hemorrhage, perforation/peritonitis, and growth failure were not more frequent in those patients (Table 1).

Surprisingly, CD patients without folate deficiency revealed a higher prevalence of osteoporosis/osteopenia (17.7 % vs 36.7 %, P < 0.001) and malabsorption syndrome (3.9 % vs 11.7 %, P = 0.005). In UC patients, we did not detect a significant association with any extraintestinal complication. CD

patients ever treated with anti-TNF antibodies (34.1 % vs 48.3 %, $P = 0.027$), currently treated with antibiotics (4.3 % vs 13.3 %, $P = 0.002$), or steroids (28.1 % vs 43.3 %, $P = 0.013$) had a lower rate of folate deficiency. For UC/IC patients no such differences were found between patients with or without folate deficiency. Further details are shown in Table 1. In both groups, we did not detect a significant difference with respect to supplementation therapy.

Vitamin B12 Deficiency in IBD Patients

Vitamin B12 levels were documented for 914 CD and 545 UC/IC patients in the SIBDCS database. Out of 914 CD patients, 163 (17.8 %) suffered from vitamin B12 deficiency. Older patients (median 42 years vs 38 years, $P = 0.027$) and smokers (45.1 % vs 33.8 %, $P = 0.007$) had a higher incidence for a vitamin B12 deficiency. In the UC/IC group a total of 545 patients were analyzed, of whom 45 (8.2 %) had a vitamin B12 deficiency. There was no significant association with age, BMI,and smoking status (Table 2, Supplementary Figures 3, 4).

Vitamin B12 deficiency was associated with a higher disease activity at enrollment according to CDAI (48 vs 35, $P = 0.041$) and more frequent complications, in particular stenosis (42.9 % vs 32.8 %, $P = 0.013$) and intestinal surgery (46 % in CD patients 33 %, $P = 0.002$) in CD patients. For UC patients, no relationship between a specific disease location and vitamin B12 deficiency was detected (Table 2).

As shown in Table 2, nephrolithasis was significantly associated with vitamin B12 deficiency in CD patients (6.1 % vs 2.8 %, $P = 0.033$). Furthermore, CD patients with vitamin B12 deficiency significantly more often suffered from iron-deficiency- related anemia (26.4 % vs 21.3 %, $P = 0.012$). CD patients under current treatment with anti-TNF antibodies had a lower rate of vitamin B12 deficiency (29.6 % vs 21.5 %, $P = 0.037$). In contrast UC/IC patients under 5-ASA therapy showed a higher rate of vitamin B12 deficiency (82.2 % vs 67.8 %, $P = 0.045$). Further details are listed in Table 2.

Anemia According to Hemoglobin Levels

We next analyzed our data as a prevalence of iron-deficiency anemia in relation to patient's hemoglobin level. There were 305 (19.6 %) CD patients and 239 (21.6 %) UC patients who were found to suffer from an iron-deficiency anemia according to our definition. In the CD group, 46.9 % male and 53.1 % female suffering from iron- deficiency anemia showed a significantly lower BMI (22.0 kg/m^2 vs 23.2 kg/m^2, $P < 0.001$) and were more often nonsmokers (21% vs 16.5% smokers). UC patients (56.1 % male and 43.9 % female) with anemia had a significantly lower BMI (22.6 kg/m^2 vs 23.9 kg/m^2, $P < 0.001$). Smoking status had no influence on anemia (Table 3, Supplementary Figures 5,6.

In the CD group, the highest prevalence of iron-deficiency anemia was detected among patients suffering from an ileocolonic disease, followed by ileal and colonic localization of the disease. CDAI score was definitely higher in patients suffering from iron-deficiency anemia (53 vs 34, $P < 0.001$). Intestinal stenosis (41.3 % vs 31.7 %, $P = 0.001$) and fistula (17.1% vs 11.1%, $P = 0.004$) had a significantly higher rate in anemic patients. In the UC/IC group, patients with pancolitis showed a higher prevalence of iron- deficiency anemia, followed by patients with left-sided colitis and proctitis. Anemic patients showed a significantly higher MTWAI score than patients without anemia (4 vs 2, $P < 0.001$). No significant association with a higher need of surgery was found between anemic and non-anemic patients (Tables 3, 4).

In CD patients with iron-deficiency anemia, we found a higher prevalence of malabsorption syndrome (6.2 % vs 3.5 %, $P = 0.031$) and more GI haemorrhage (2.6 % vs 0.7 %, $P = 0.004$). Furthermore, anemic patients suffered from a significantly higher rate of disease complications, such as fistula (17.1 % vs 11.1 % $P = 0.004$) and stenoses (41.3 % vs 31.7 %, $P = 0.001$). Further details are depicted in Table 3. As shown in Table 4 UC/IC patients with iron-deficiency anemia suffered significantly more from deep venous thrombosis (5.9 % vs 1.5 %, $P < 0.001$) and malabsorption syndrome (3.8 % vs 0.8 %, $P = 0.001$). UC patients with iron-deficiency anemia showed a significantly higher rate of erythema nodosum occurrence when compared with UC patients without iron-deficiency anemia (6.3% vs 2.1%, $P = 0.001$).

CD patients with iron-deficiency anemia significantly more often received steroids (40 % vs 27 %, $P < 0.001$) and antibiotics (8.9 % vs 3.5 %, $P < 0.001$) compared to patients without anemia. UC/IC patients with iron-deficiency anemia also consumed significantly more often steroids (52.7 % vs 28.8 %, $P < 0.001$), antibiotics (5.9 % vs 1.8 %, $P = 0.001$), and anti-TNF antibodies (17.2 % vs 11.9 %, $P = 0.031$). No significant difference was found for other medications, such as mesalazine and immunosuppressants, eg, azathioprine or 6-mercaptopurin, in both, the CD and the UC group (Tables 3 , 4).

Anemia According to Ferritin Levels in IBD Patients

We finally analyzed the prevalence of anemia in relation to the patient's iron status in CD and UC patients (Tables 5, 6, Supplementary Figs. 7, 8). Out of 1011 CD patients, 263 (26 %) had an anemia with a ferritin level < 30 µg/l. Patients with anemia had a lower BMI (21.9 kg/m^2 vs 23.2 kg/m^2, $P < 0.001$) and were younger by diagnosis and during enrollment. In UC/IC group (Table 6) from a total of 713 patients, 220 (30.8 %) had an anemia with ferritin level < 30 µg/l. Anemic UC patients also had a lower BMI (22.8 kg/m^2 vs 23.6 kg/m^2, $P < 0.001$) and were younger than patients without anemia. Smoking status did not have a significant influence on iron-deficiency anemia in both the CD and the UC groups.

TABLE 1: Folate Deficiency in Relation to Significant Patients Characteristics in Crohn's Patients and UC Patients (n: Total Number of Patient for Each Group)

CD Only	No Folate Deficiency (n = 60 patients)	Folate Deficiency (n = 695 patients)	*P* value
Smoking status at diagnosis			
Non-smoker	39 (66.1)	329 (48.4)	
Smoker	20 (33.9)	351 (51.6)	0.009
Initial CD location			
L1 (ileal)	5 (8.3)	182 (26.2)	
L2 (colonic)	11 (18.3)	151 (21.7)	
L3 (ileocolonic)	35 (58.3)	301 (43.3)	
L4 (Upper GI only)	2 (3.3)	5 (0.7)	
Unknown/unclear	7 (11.7)	56 (8.1)	0.002
Current CD location			
L1 (ileal)	12 (20.0)	220 (31.7)	
L2 (colonic)	15 (25.0)	208 (29.9)	
L3 (ileocolonic)	28 (46.7)	242 (34.8)	
L4 (Upper GI only)	4 (6.7)	5 (0.7)	
Unknown/unclear	1 (1.6)	20 (2.9)	0.003
Other Fistula	16 26.7)	83 (11.9)	0.001
Fistula/abscess surgery.	18 (30.0)	131 (18.9)	0.037
Therapy (Ever treated)			
Anti-TNF	29 (48.3)	237 (34.1)	0.027
Current Therapy			
Antibiotics	8 (13.3)	30 (4.3)	0.002
Steroids	26 (43.3)	195 (28.1)	0.013
Anti-TNF	22 (36.7)	172 (24.8)	0.043
Complications			
None	20 (33.3)	409 (58.9)	
Yes	40 (66.7)	286 (41.2)	*<0.001*
Osteoporosis/Osteopenia	*22 (36.7)*	*123 (17.7)*	*<0.001*
Anemia	*26 (43.3)*	*126 (18.1)*	*<0.001*
Malabsorption syndrome.	*7 (11.7)*	*27 (3.9)*	*0.005*
Supplementation therapy			
Calcium	27 (45.0)	194 (27.9)	0.005
Potassium	4 (6.7)	9 (1.3)	0.015
Vitamin D	26 (43.3)	167 (24.0)	0.001
UC/IC ONLY	No Folate Deficiency (26 patients)	Folate Deficient (454 patients)	*P*-value
Smoking status at diagnosis			
Nonsmoker	25 (96.2)	353 (79.2)	
Smoker	1 (3.8)	93 (20.9)	0.040
Complications			
Anemia	*11 (42.3)*	*88 (19.4)*	*0.005*

Anemic patients in both groups had a more active disease with a higher CDAI and MTWAI score, respectively, in comparison to non-anaemic patients (CD patients: 48 vs 39, $P = 0.013$; UC/IC patients: 6 vs 2, $P < 0.001$). For further details, see Tables 5 and 6. Surgical procedures in UC/IC patients were more frequently among the non-anaemic group when compared with anemic patients (3.7 % vs 0.9 %, $P = 0.048$).

CD patients with iron-deficiency anemia (as listed in Table 5) suffered significantly more often from uveitis/iritis (9.5 % vs 5.5 %, $P = 0.023$) and erythema nodosum (9.1 % vs 4.6 %, $P = 0.006$). Whereas anemic UC/IC patients had a higher incidence of arthritis (28.6 % vs 20.9 %, $P = 0.024$), iron anaemic CD patients significantly had more folate and vitamin B12 deficiency (folate deficiency $P = 0.025$, vitamin B12 deficiency $P = 0.024$).

TABLE 2: Vitamin B12 Deficiency in Relation to Significant Patients Characteristics (n: Total Number of Patient for Each Group)

CD Only	No Vitamin B12 Deficiency (n = 751 patients)	Vitamin B12 Deficiency (n = 163 patients)	*P*value
Age at enrollment (y) (median, IQR; range)	38, 27–51; 16–88	42, 30–55; 18–77	0.027
Smoking status at enrollment			
Nonsmoker	487 (66.2)	89 (54.9)	
Smoker	249 (33.8)	73 (45.1)	0.007
Current CD location			
L1 (ileal)	223 (29.7)	60 (36.8)	
L2 (colonic)	241 (32.1)	29 (17.8)	
L3 (ileocolonic)	257 (34.2)	66 (40.5)	
L4 (Upper GI only)	11 (1.5)	1 (0.6)	
Unknown/unclear	19 (2.5)	7 (4.3)	0.002
CDAI at enrollment (median, IQR; range)	35, 14–76; 0–450	48, 23–88; 0–280	0.041
Stenosis	246 (32.8)	70 (42.9)	0.013
Intestinal surgery	248 (33.0)	75 (46.0)	0.002
Current Therapy			
Anti-TNF	222 (29.6)	35 (21.5)	0.037
Complications			
Pyoderma gang.	*45 (6.0)*	*3 (1.8)*	*0.032*
Nephrolithiasis	*21 (2.8)*	*10 (6.1)*	*0.033*
Supplementation therapy			
Vitamin B12	155 (20.6)	55 (33.7)	<0.001
Anemia (iron)			
None	516 (76.4)	100 (67.6)	
Iron with active IBD	15 (2.2)	9 (6.1)	
Iron	144 (21.3)	39 (26.4)	0.012
UC/IC ONLY	No Vit B12 Deficiency (n = 500 patients)	Vit B12 Deficiency (n = 45 patients)	*P*-value
Current Therapy			
5-ASA	339 (67.8)	37 (82.2)	0.045
Complications			
None	333 (66.6)	34 (75.6)	
Yes	167 (33.4)	11 (24.4)	0.220
CRCr	*3 (0.6)*	*0 (0.0)*	*1.000*
Colonic Dysplasia	*6 (1.2)*	*0 (0.0)*	*1.000*
Osteoporosis/Osteopeni	*61 (12.2)*	*4 (8.9)*	*0.636*
Anemia Deep Venous	*100 (20.0)*	*7 (15.6)*	*0.472*
Thromb	*16 (3.2)*	*0 (0.0)*	*0.385*
Pulmonary Embolism	*9 (1.8)*	*0 (0.0)*	*1.000*
Gallstone	*10 (2.0)*	*1 (2.2)*	*1.000*
Nephrolitiasis	*14 (2.8)*	*1 (2.2)*	*1.000*
Malabsorption syndrome	*9 (1.8)*	*1 (2.2)*	*0.581*
Massive Hemorrage	*8 (1.6)*	*0 (0.0)*	*1.000*
Perforation/Peritonitis	*3 (0.6)*	*0 (0.0)*	*1.000*
Growth failure	*0 (0.0)*	*0 (0.0)*	-
Supplementation therapy			
Iron	84 (16.8)	13 (28.9)	0.042
Vitamin B12	26 (5.2)	9 (20.0)	<0.001

TABLE 3: Anemia (Defined by Low Hemoglobin Levels) in Relation to Significant Patients Characteristics (n: Total Number of Patient for Each Group)

CD Only	No Anemia (Hb) (n = 1253 patients)	With Anemia (Hb) (n = 305 patients)	*P* value
BMI (median, IQR; range)	23.2, 20.8-26.2	22.0, 19.6-24.8	
	14.0-48.1	13.9-43.4	<0.001
Smoking status at enrollment			
Nonsmoker	770 (62.9)	210 (70.0)	
Smoker	454 (37.1)	90 (30.0)	0.022
CDAI at enrollment (median, IQR; range)	34, 13-74	53, 26-101	
	0-450	6-296	<0.001
Other Fistula	139 (11.1)	52 (17.1)	0.004
Stenosis	397 (31.7)	126 (41.3)	0.001
Therapy (Ever treated)			
Steroids	1007 (80.4)	267 (87.5)	0.004
Current Therapy			
Antibiotics	44 (3.5)	27 (8.9)	<0.001
Steroids	338 (27.0)	122 (40.0)	<0.001
Anti-TNF	432 (34.5)	87 (28.5)	0.048
Complications			
Yes	*427 (34.1)*	*162 (53.1)*	*<0.001*
Anemia	*156 (12.5)*	*110 (36.1)*	*<0.001*
Malabsorption syndrome	*44 (3.5)*	*19 (6.2)*	*0.031*
Massive Haemorrhage	*9 (0.7)*	*8 (2.6)*	*0.004*
Supplementation therapy			
Calcium	321 (25.6)	124 (40.7)	<0.001
Iron	138 (11.0)	81 (26.6)	<0.001
Potassium	7 (0.6)	8 (2.6)	0.001
Vitamin D	289 (23.1)	103 (33.8)	<0.001
Anemia (iron)			
None	626 (77.3)	116 (61.1)	
Iron with active IBD	25 (3.1)	6 (3.2)	
Iron	159 (19.6)	68 (35.8)	<0.001

In the CD group (Table 5), anemia was not associated with the use of any medication. In contrast UC/IC patients with iron-deficiency anemia more frequently used immunomodulators (63.6 % vs 51.9 %, $P = 0.004$), anti-TNF antibodies (26.8 % vs 15 %, $P < 0.001$), and steroids (42.7 % vs 28.4 %, $P < 0.001$). In the CD group, patients suffering from anemia more often used supplementation therapies than patients without anemia, in particular supplementation of calcium (40.7 % vs 25.6 %), iron (26.6 % vs 11 %), potassium (2.6 % vs 0.6 %), and vitamin D (33.8 % vs 23.1 %). A similar result was observed among UC patients in that calcium (41.8% vs 25.1%), iron (27.2% vs 13.8%), and vitamin D (36% vs 22.8%) supplementation therapy was more common among anemic patients (Tables 5 , 6).

DISCUSSION

In the present study we aimed at analyzing prevalence and consequences of vitamin and iron deficiency in patients of the SIBDCS. In line with current literature data about healthy populations,[24, 25] smoking was clearly associated with folate and vitamin B12 deficiency in our SIBDCS patient collective. This finding can be explained by the observation that smokers consume less amounts of foods that are rich in antioxidants and tend to prefer a dietary pattern that is rich in meat and alcohol.[26–28] A recent meta-analysis by Burr et al showed that folic acid supplementation decreases the risk of CRC in patients with IBD[29] and those data were confirmed by another study monitoring homocysteine levels.[30] Some studies have shown that CD itself is a risk factor for folate deficiency, mainly because of the ileal location of the disease, with an overall prevalence between 0%–60 %.[16, 31, 32] In our cohort, the overall prevalence of vitamin B12 and folic acid deficiency was higher than in other studies, in particular from the US and Canada. This observation might be linked to the fact that our cohort is primarily part of a tertiary referral center. On the other

TABLE 4: Anemia (Defined by Low Hemoglobin Levels) in Relation to Significant Patients Characteristics (n: Total Number of Patient for Each Group)

UC/IC Only	No Anemia (Hb) (n = 869 patients)	With Anemia (Hb) (n = 239 patients)	*P*value
Disease duration (y) (median, IQR; range)	6, 2-13	5, 1-11	
	0-50	0-34	0.006
BMI (median, IQR; range)	23.9, 21.7-26.6	22.6, 20.6-25.1	
	16.7-48.8	15.1-38.0	<0.001
Initial UC/IC location			
Pancolitis	333 (38.7)	109 (45.8)	
Left-sided colitis	287 (33.3)	73 (30.7)	
Proctitis	167 (19.4)	30 (12.6)	
Unknown/unclear	74 (8.6)	26 (10.9)	0.034
Current UC/IC location			
Pancolitis	349 (40.2)	133 (55.7)	
Left-sided colitis	352 (40.5)	84 (35.2)	
Proctitis	144 (16.6)	17 (7.1)	
Unknown/unclear	24 (2.8)	5 (2.1)	<0.001
MTWAI at enrollment (median, IQR; range)	2, 1-5	4, 2-8	
	0-19	0-16	<0.001
Therapy (Ever treated)			
Steroids	653 (75.1)	196 (82.0)	0.026
Immunomodulators	483 (55.6)	150 (62.8)	0.047
Anti-TNF	161 (18.5)	65 (27.2)	0.003
Current Therapy			
Antibiotics	16 (1.8)	14 (5.9)	0.001
Steroids	250 (28.8)	126 (52.7)	<0.001
Anti-TNF	103 (11.9)	41 (17.2)	0.031
EIM			
Yes	*27 (3.1)*	*15 (6.3)*	*0.001*
Arthritis/arthralgia	*23 (2.7)*	*15 (6.3)*	*0.023*
Uveitis/Iritis		*1 (0.4)*	*0.041*
Complications			
None	633 (72.8)	120 (50.2)	
Yes	236 (27.2)	119 (49.8)	<0.001
Osteoporosis/Osteopen.	*99 (11.4)*	*43 (18.0)*	*0.007*
Anemia Deep Venous	*117 (13.5)*	*88 (36.8)*	*<0.001*
Thromb	*13 (1.5)*	*14 (5.9)*	*<0.001*
Malabsorption syndrome.	*7 (0.8)*	*9 (3.8)*	*0.001*
Supplementation therapy			
Calcium	218 (25.1)	100 (41.8)	<0.001
Iron	120 (13.8)	65 (27.2)	<0.001
Vitamin D	198 (22.8)	86 (36.0)	<0.001
Anemia (iron)			
None	418 (73.9)	71 (51.1)	
Iron with active IBD	55 (9.7)	22 (15.8)	
Iron	93 (16.4)	46 (33.1)	<0.001

TABLE 5: Iron-Deficiency Anemia in Relations to Patients Significant ($P < 0.05$) Characteristics (n: Total Number of Patient for Each Group)

CD Only	No Anemia (Iron) (n = 748 patients)	With Anemia (Iron) (n = 263 patients)	*P* value
Gender			
Male	381 (50.9)	93 (35.4)	
Female	367 (49.1)	170 (64.6)	<0.001
Age at diagnosis (y) (median, IQR; range)	27, 20-37	23, 18-32	
	1-81	5-78	<0.001
Age at enrollment (y)(median, IQR; range)	39, 28-52	33, 24-44	
	16-88	17-85	<0.001
BMI (median, IQR; range)	23.2, 20.8-26.3	21.9, 19.9-25.2	
	13.9-48.1	14.6-43.4	<0.001
CDAI at enrollment (median, IQR; range)	39, 17-76	48, 17-95	
	0-435	0-388	0.013
EIM			
None	443 (59.2)	149 (56.7)	
	305 (40.8)	114 (43.4)	0.467
Yes	*238 (31.8)*	*84 (31.9)*	*0.971*
	41 (5.5)	*25 (9.5)*	*0.023*
	7 (0.9)	*5 (1.9)*	*0.214*
Arthritis/arthralgia	*34 (4.6)*	*24 (9.1)*	*0.006*
Uveitis/Iritis	*57 (7.6)*	*21 (8.0)*	*0.849*
Pyoderma gang.	*38 (5.1)*	*9 (3.4)*	*0.272*
	3 (0.4)	*1 (0.4)*	*1.000*
Erythema nodosum	*26 (3.5)*	*5 (1.9)*	*0.203*
Complications			
Yes	*387 (38.4)*	*129 (49.0)*	*0.002*
Folate deficiency	475 (90.8)	171 (96.1)	0.025
Anemia (Hb)	116 (15.6)	74 (28.7)	<0.001
Vit B12 deficiency	100 (16.2)	48 (23.2)	0.024

hand, lower rates in US and Canadian studies can likely also be explained with local folic acid fortification practices, since fortification with folic acid is not routinely done to a comparable extent in Switzerland, as eg, in the US. Nevertheless, folic acid and vitamin B12 supplementation must be considered in IBD patients with folate deficiency, especially in UC patients who show a higher incidence of CRC.[33] Steroid therapy and anti-TNF treatment are associated with normal folate levels, possibly because of their anti-inflammatory action on the intestinal mucosa, thus providing a better reabsorption at the intestinal level.[34] A similar conclusion can be drawn for vitamin B12, in particular because of the closely related way of absorption and the strictly connected metabolic pathways.[31] Of note, also CD patients with current antibiotic treatment significantly more often show normal folate levels. This might be explained by a better disease control in those patients (similar to patients with steroid or anti-TNF therapy) than by the onset of SIBO due to IBD surgeries, since intestinal surgery in patient's history is not associated with higher folate levels and bacterial overgrowth (which would be reduced by typical antibiotics used in CD, eg, metronidazole) that would rather increase folate levels with concomitant decrease in vitamin B12 levels.

IBD patients with anemia have a significantly lower BMI than patients without anemia. This finding is in line with the literature: subjects with normal BMI showed normal hemoglobin levels and less tendency to develop anemia.[35, 36] Of note, smoking is clearly associated with folate and vitamin B12 deficiency in our SIBDCS patients. However, surprisingly, nonsmoking status is positively associated with anemia in CD patients. This might be due to the fact that smokers show in general a trend towards higher hemoglobin levels compared to nonsmokers, which t can be explained by the well-studied reactive hemoglobine hyperproduction in smokers.[37, 38] Based on this explanation we hypothesize that the anemia rate in smoking CD patients is affected by higher hemoglobin levels due to smokingthat finally results in our observation that smoking is, in contrast to nonsmoking, not associated with anemia. Anemia is more common

TABLE 6: Iron-Deficiency Anemia in Relation to Significant Patients Characteristics (n: Total Number of Patient for Each Group)

UC/IC Only	No Anemia (Iron) (n = 493 patients)	With Anemia (Iron) (n = 220 patients)	*P* value
Age at diagnosis (y) (median, IQR; range)	32, 24-41	27, 21-36	
	10-82	9-71	<0.001
Age at enrollment (y) (median, IQR; range)	41, 31-52	36, 27-44	
	17-84	15-73	<0.001
BMI (median, IQR; range)	23.6, 21-3-26.3	22.8, 20.7-25.3	
	15.1-48.8	16.7-38.4	0.014
Initial UC/IC location			
Pancolitis	191 (39.0)	91 (41.7)	
Left-sided colitis	153 (31.2)	82 (37.6)	
Proctitis	102 (20.8)	25 (11.5)	
Unknown/unclear	44 (9.0)	20 (9.2)	0.023
MTWAI at enrolment (median, IQR; range)	2, 1-4	6, 2-9	
	0-19	0-15	<0.001
Intestinal surgery	24 (4.9)	21 (9.6)	0.018
Therapy (Ever treated)			
Anti-TNF	74 (15.0)	59 (26.8)	<0.001
Immunomodulators	256 (51.9)	140 (63.6)	0.004
Current Therapy Steroids	140 (28.4)	94 (42.7)	<0.001
EIM			
Yes	103 (20.9)	63 (28.6)	0.024
Erythema nod.	18 (3.7)	2 (0.9)	0.048
Complications			
Yes	*142 (28.8)*	*86 (39.1)*	*0.007*
Anemia	*78 (15.8)*	*59 (26.8)*	*0.001*
Supplementation therapy			
Iron	71 (14.4)	62 (28.2)	<0.001
Mutaflor	18 (3.7)	19 (8.6)	0.006
Anemia (Hb)	71 (14.5)	68 (31.5)	<0.001

in CD patients suffering from intestinal stenosis and fistula.[39] The higher disease severity in anemic CD patients as demonstrated by significantly higher levels of CDAI can be explained by the fact that anemia in general leads to symptoms such as fatigue, failure to thrive, etc. On the other hand, a higher disease activity is known to be associated with anemia, as previously reported in the literature for CD patients.[40, 41] Malabsorption syndrome and massive hemorrhage were more common in anemic CD patients. This finding can be explained as one of the causes of anemia might be malabsorption of iron from the intestine and loss of blood. Nevertheless, it is difficult to assess whether the primary cause of anemia in those patients is blood loss from the GI tract or the reduced absorption of iron.

A very interesting finding of our study was the observation that UC patients ever treated with anti-TNF antibodies showed a lower tendency to develop anemia. This observation may be linked to the finding that chronic inflammatory anemia is supported by inflammatory cytokines, particularly TNF that affects iron metabolism.[42, 43] The same observation was made for treatment with steroids that also act as anti-inflammatory drugs and repress cytokine formation (thus repressing anemia of chronic disease). There are divergent opinions regarding the effect of anti-TNF antibodies on anemia of chronic disease, especially in IBD. Whereas a recent study from Koutroubakis et al showed no improvement of anemia after 1 year of treatment,[44] Bergamaschi et al found a significant improvement of hemoglobin levels.[40] To date, there are many controversies about anti-TNF treatment and anemia resolution, and thus further studies are necessary to assess this issue in more detail. In the UC group, anemia quantified as ferritin levels showed an improvement under immunomodulatory therapy. Of note, about 60 % of IBD patients do not tolerate the oral form of iron substitution.[45] If the anemia is severe (<10 g/L) or if there are factors that indicate a complicated disease course,

intravenous iron substitution should be definitely taken into account.[19, 46]

Furthermore, we observed that anemic patients are likely to exhibit micronutrient deficiency. This should prompt the treating physicians to carefully check other micronutrient laboratory values, when anemia is diagnosed. Patients suffering from anemia tend to have multiple supplementation therapies (calcium, potassium, and vitamin D) besides iron supplementation. This can be observed when analyzing CD and UC patients. Unfortunately, to date supplementation therapy in IBD patients is not a common practice in daily patient care. However, t because inflammation and common disease complications, such as strictures or intestinal surgery, lead to a loss of important gut segments,[2, 47] deficiencies of micronutrients, vitamins, and minerals are a common problem in IBD patients.[48] Therefore, vitamin and iron levels should be regularly monitored and deficiencies need to be treated to prevent complications and to improve the disease course. A further important preventive measure in the management of IBD patients is providing a fiber-rich diet that may play a role in maintaining remission in those patients, reducing the risk of a more severe disease course, and CRC development. Indeed, a high dietary fiber intake has even been shown to be negatively associated with the risk of developing CD (but not UC) in a very large prospective study from the US.[49] As possible mode of actions, it is hypothesized that dietary fibers directly interact with the intestinal microbiome, eg, by modulating intestinal immune responses or by directly affecting intestinal microbiota composition.[20] Therefore, based on the literature, a fiber-rich diet seems to have beneficial effects for IBD patients and should be promoted by the treating physicians.

In the Filmann et al study 2192 patients from all across Europe were included.[6] In contrast, our study seems herein to be superior in a way that we were able to include 2666 IBD patients alone from Switzerland. The overall prevalence of anemia in IBD patients in the Filman study was 24 %, being 57 % of those patients were iron deficient. In our study, iron-deficiency anemia was detected in 19.6 % of CD patients and 21.6 % of UC patients. This suggests that iron-deficiency anemia might be a little bit more frequent than compared to the whole of Europe. However, this observation might be related to the clear strength of our study: we present data of a large and very well-characterized patient collective that has been treated according to comparable guidelines. In contrast, the European collective, put together based on a literature search, represents patients from a broad number of countries who have most likely been treated according to different guidelines that makes data interpretation difficult. It might be that iron substitution is started according to very different guidelines in different European countries that might critically affect comparability of the data. Therefore, our study represents a large and in the end likely homogeneously treated patient collective that adds critical value to the obtained findings. As a result our data might contribute to daily clinical practice, since these findings suggest that regular monitoring and substitution of vitamins and iron should be mandatory and may prevent long-term intestinal and extraintestinal complications in IBD patients.

CONCLUSIONS

In summary, our data support that folate, vitamin B12, and iron levels in patients suffering from IBD regardless of the subtype should be monitored routinely. In the case of vitamin deficiency, a substitution therapy needs to be established, thus preventing a complicated disease course. Furthermore, future investigations are needed to assess a possible link between current long-term medical treatment and/or nutrient deficiencies to optimize patient care.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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