Iron Deficiency in the Absence of Anemia Impairs the Perception of Health-Related Quality of Life of Patients with Inflammatory Bowel Disease

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Background: Anemia is a common complication of inflammatory bowel disease (IBD) and contributes to the deterioration of health-related quality of life (HRQOL). Iron deficiency (ID) is a prevalent underlying factor, present in up to 90% of patients. In the absence of anemia, it is unclear as to what extent ID can affect HRQOL in patients with IBD. Our aim was to determine whether ID without anemia negatively affects normal perception of HRQOL in patients with IBD in remission.

Methods: We conducted a prospective, cross-sectional study in patients with IBD in remission without anemia. Blood samples were obtained to determine iron status, and patients completed the Inflammatory Bowel Disease Questionnaire-36. ID was defined on serum ferritin <30 ng/mL and transferrin saturation $<16\%$. Restoration of HRQOL was defined as ≥ 209 on the Inflammatory Bowel Disease Questionnaire-36.

Results: One hundred-four patients with IBD in clinical remission were included; 45 patients were iron deficient and 59 had normal iron status. All patients were in clinical remission, with a median Harvey–Bradshaw Index ≤ 0 and Simple Clinical Colitis Activity Index ≤ 0. Median hemoglobin was 12.8 g/dL in the ID group and 13.9 g/dL in the normal iron status group ($P < 0.05$). Prevalence of female patients was higher in the ID group (odds ratio, 4.45; 95% CI, 1.7–11.7; $P < 0.01$). The median global value of Inflammatory Bowel Disease Questionnaire-36 was not different between the groups (219 in the ID group versus 230 in the normal iron status group, $P =$ not significant), but restoration of health was significantly less frequent in patients with ID (odds ratio, 2.83; 95% CI, 1.22–6.6; $P < 0.05$).

Conclusions: ID in absence of anemia negatively impacts normal perception of HRQOL in patients with IBD in remission. Correction of ID may be a new target in the treatment of these patients.

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Key Words: inflammatory bowel disease, iron deficiency, health-related quality of life

Health-related quality of life (HRQOL) is impaired in inflammatory bowel disease (IBD), resulting in considerable impact in all aspects of a patient's life.[1] HRQOL is a multidimensional construct composed of physical, social, and psychological functioning, overall satisfaction and well-being, and subjective perceptions of health status.[2] There are several well-known factors that influence the HRQOL in patients with IBD that include disease activity, prolonged treatment and the adverse effects associated with such treatment, and the need for surgery and hospitalization among others.[3] Anemia is one factor that has a significant detrimental impact on the quality of life of patients with IBD.[4]

The World Health Organization defines anemia as hemoglobin concentration <12 g/dL for nonpregnant women and <13 g/dL for men. The prevalence of anemia has been estimated to be between 6% and 73% and varies between subpopulations, with a higher prevalence at diagnosis and in patients with Crohn's disease (CD).[5,6]

Anemia in patients with IBD has multiple causes, such as anemia of chronic disease, inadequate dietary intake or malabsorption of vitamin B12 and folate, and drug toxicities.[7] But the most prevalent cause is iron deficiency (ID) as a consequence of intestinal bleeding, dietary restrictions, or malabsorption.[6,8] ID anemia is a severe stage of ID in which hemoglobin declines below the lower limit of normal with biochemical evidence of ID.

Iron is a biologically essential component of every living organism. Two-thirds of body iron is found in hemoglobin in circulating erythrocytes, 25% in iron store, and the remaining 15% bound to myoglobin in muscle tissue Choudhuryand in a variety of enzymes involved in cell functions. Iron absorption occurs by the enterocytes, predominantly in the duodenum and

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upper jejunum. Ferritin concentration together with that of hemosiderin reflects body iron stores. Iron is highly conserved and not readily lost from the body.[9]

ID is the most common nutritional deficiency worldwide.[10] Appropriate criteria for ID in patients with IBD without biochemical or clinical evidence of inflammation are a serum ferritin <30 ng/mL and/or a transferrin saturation <16%.[11,12] ID without anemia is the reduction of the total iron content of the body, with normal levels of hemoglobin. A systematic review identified ID as a contributing factor for fatigue in patients with IBD.[13] ID without anemia has been associated with fatigue and impaired exercise capacity in otherwise healthy populations.[14,15]

Anemia has a significant detrimental impact on the quality of life of patients with IBD.[16] Observational studies of iron replacement demonstrate a positive correlation between an increase in hemoglobin (Hb) level and quality of life–questionnaire scores, independent of changes in disease activity.[17,18] However, in the absence of anemia, it is unclear as to what extent ID can contribute to a deterioration of HRQOL in patients with IBD.

A recent study that evaluated the effect of ID and/or anemia on HRQOL in patients with chronic heart failure found that ID, but not anemia, was associated with reduced HRQOL in these patients.[19] No study to date has directly evaluated patients with IBD with and without ID in the absence of anemia in terms of patient-centered outcomes. The aim of the present study was to evaluate the influence of ID without anemia on the perception of HRQOL in patients with IBD in clinical remission. To analyze the subjective repercussion of ID, we also assessed the presence of fatigue in these patients.

MATERIALS AND METHODS

Patients

A prospective, observational, cross-sectional study was conducted in adult patients with IBD. Diagnosis of IBD was established by conventional clinical, endoscopic, radiological, and histological criteria. Subjects included in the study had IBD, either CD or ulcerative colitis (UC) and had been diagnosed and treated in our unit. Blood samples were obtained before inclusion as part of their usual clinical follow-up, and the status of anemia and ID was determined. Patients were in clinical remission, were at least 18 years of age, did not have anemia according to World Health Organization criteria, and had given consent to participate in this study. Demographic and clinical data were collected. All patients completed the specific questionnaire of quality of life Inflammatory Bowel Disease Questionnaire (IBDQ)-36 and the Daily Fatigue Impact Scale questionnaire. Patients who were receiving iron supplements at the time of inclusion were excluded from the study.

Assessment of Disease Activity

Current disease activity was determined based on standardized clinical indexes obtained during the clinical interview using the Harvey–Bradshaw Index and the Simple Clinical Colitis Activity Index. To be included in the study, patients had to be on clinical remission defined as a Harvey–Bradshaw score lower than 4 points and a Simple Clinical Colitis Activity Index less than 4 points for patients with CD and UC, respectively. We also determined C-reactive protein, with a normal cutoff value of <0.5 mg/dL for remission.

Assessment of Quality of Life

HRQOL of patients was assessed using the IBDQ-36. This is a disease-specific self-administered questionnaire that has been translated and validated for its use in Spain.[20] This version includes 36 items that are grouped into 5 domains of health (bowel symptoms, systemic symptoms, functional impairment, social impairment, and emotional function). Responses are scored on a 7-point Likert scale, in which 7 corresponds to the highest level of functioning. The instrument produces five dimension scores and an overall IBDQ score ranging from 36 to 252, where a higher score reflects better HRQOL. According to previously validated criteria, perceived health was considered restored to normal when the overall score of IBDQ-36 was equal or greater than 209.[21]

Assessment of Fatigue

To analyze the subjective repercussion of ID, we also assessed the presence of fatigue in these patients. The Daily Fatigue Impact Scale is a one-dimensional scale that contains 8 items with 5 options each, so that the total score ranges from 0 to 32, where a higher score indicates more severe fatigue.[22] It has been adequately translated and validated to Spanish and correlates with clinical activity and the IBDQ-36 in patients with IBD.[23]

Assessment of Iron Status

In this study, ID without anemia was defined on the basis of laboratory assay standards as serum ferritin <30 ng/mL and transferrin saturation <16%, with a normal hemoglobin. Subjects were classified as either iron deficient (both ferritin <30 ng/mL and transferrin saturation <16%) or iron sufficient (ferritin ≥30 ng/mL and/or transferrin saturation ≥16%). Patients with anemia, defined as serum Hb value less than 13 g/dL in men and less than 12 g/dL in women, per usual laboratory parameters, were not included in the study. Pregnant patients were also excluded from the study.

Statistical Analysis

The statistical analysis was conducted with IBM SPSS Statistics for MAC, Version 20.0. Armonk, NY: IBM Corp. According to the Kolmogorov–Smirnov test, variables were not normally distributed. Thus, results are expressed as percentages or medians, and percentiles. Fisher's exact test was performed for categorical variables and Mann–Whitney U test for quantitative variables. To control for confounding, we performed a regression analysis. A 2-tailed $P < 0.05$ was considered statistical significant.

RESULTS

Characteristics of Patients

A total of 104 patients with IBD were included. Median age was 36 (31–44) and 69% (n = 74) were women. Fifty-six percent (n = 58) had Crohn's disease (CD) and the rest (n = 46) had UC. All were in clinical remission, with a median Harvey–Bradshaw score of 0 (0–1) for patients with CD and a Simple Clinical Colitis Activity Index of 0.5 (0–2) for UC. Median hemoglobin was 12.8 g/dL (12.3–13.5) for women and 14.8 (14–15.5) for men.

Iron Deficiency

As shown in Table 1, 43% (n = 45) of patients had ID with normal Hb values, with a median ferritin of 15 ng/mL (13–20), transferrin saturation of 14% (12–15.5), and serum iron of 42 mcg/dL (36–68). Eighty-six percent (n = 39) of iron-deficient patients were women (odds ratio [OR], 4.45; 95% CI, 1.7–11.7; $P < 0.01$) with no difference in the type of IBD, extension of disease, presence of extraintestinal manifestations, treatment, or disease duration between the ID and normal groups. Although both groups had normal hemoglobin values, iron-deficient patients had lower hemoglobin than normal iron status patients (12.8 versus 13.9 g/dL, $P < 0.05$). C-reactive protein was slightly higher in iron-deficient patients (0.3 versus 0.13 mg/dL, $P < 0.01$).

Quality of Life and Iron Status

Seventy-one patients (68%) had a normal perception of health (global IBDQ-36 score >209). Although global IBDQ-36 score was not significantly different between iron-deficient and normal iron status patients (219 versus 230, P = not significant), restoration of health was significantly less frequent in iron-deficient patients than in patients with normal iron status (OR, 2.83; 95% CI, 1.22–6.6; $P < 0.05$) (Fig. 1).

ID, female gender, ferritin, transferrin saturation, serum iron, and CPR were associated with nonnormalization on the perception of HRQOL in the univariate analysis (Table 2). In the multivariate analysis, we found a significant association between nonnormalization of the HRQOL and the presence of ID and female gender (OR, 3.41; 95% CI, 1.22–9.60 and OR, 8.27; 95% CI, 1.77–29, respectively).

Fatigue and Iron Status

As a secondary outcome of interest, we evaluated the relationship of fatigue with iron levels. Iron-deficient patients had significantly higher scores in the Daily Fatigue Impact Scale (8 versus 3, $P < 0.05$), which indicates that ID is associated with a more pronounced fatigue in these patients, even if anemia is not present.

DISCUSSION

Iron is an essential element, typically paired with hemoglobin and plays pivotal roles in immunological functions, maintaining exercise capacity, and in neurotransmitter metabolism, which maintains cognitive functions such as learning and memory. There are few studies that have analyzed the impact of ID on quality of life of patients with IBD, mostly focusing on its association with anemia.[17,24] ID without anemia has been associated with fatigue and poor quality of life even in subjects without chronic or active diseases. A large study evaluated the efficacy and tolerability of a single infusion of ferric carboxymaltose in improving fatigue symptoms, quality of life, and cognitive function in women with ID without chronic medical conditions.[25] Iron repletion reduced fatigue symptoms, improved QOL and cognitive functions in these women. Their results underscore the important role that ID plays in quality of life.

Gasche et al. published guidelines for iron and anemia in IBD,[11] and the European Crohn's and Colitis Organization recently published a consensus for the description and treatment of anemia in IBD.[12] There is no consensus on the management of ID in the absence of anemia. ID in patients with IBD has been reported to be around 40% and even as high as 80%.[26,27] Our study, although not directly designed to determine the prevalence of ID in IBD, confirms that ID is frequent, as we found that 43% of included patients were iron deficient. ID usually goes unrecognized and little is known about its clinical impact. Recent evidence supports that treatment of ID in the absence of anemia with intravenous iron improves patient's QOL as measured by the IBDQ or the short form-36 questionnaires.[28]

In this study, we aimed to investigate the relationship between ID and HRQOL in clinically quiescent IBD, in the absence of anemia. Although the global score of the IBDQ-36 did not differ between iron-deficient and normal iron status patients, when we measured the selective criterion of normalization of perception of health (IBDQ-36 score >209), we found a significant association between ID and nonnormalization of HRQOL. We also found an association between female gender and nonnormalization of HRQOL, but ID is more prevalent in menstruating women[29] and in the multivariate analysis, ID was an independent factor associated with nonnormalization of HRQOL.

As a secondary outcome, we explored the magnitude of fatigue in iron-deficient patients using the Daily Fatigue Impact Scale score and we found that iron-deficient patients had higher scores in this questionnaire when compared to normal iron status patients. Goldenberg et al.[26] have explored this association previously, and in their study, ID did not contribute to the presence of fatigue in patients with IBD. In this study, fatigue was assessed using the Multidimensional Fatigue Inventory[30] and disease activity was clinically measured using the Harvey–Bradshaw Index for CD and the Powell-Tuck Index for UC, with the cutoff level of active disease at more than or equal to 5. Because the primary outcome of our study was HRQOL and ID, we cannot generalize our findings on fatigue and ID and we believe that this should be further addressed in future studies.

TABLE 1. Characteristics of Patients According to Iron Status (Median and Interquartile Range)

n = 104	Nonanemic and Iron Deficient (n = 45)	Nonanemic and Normal Iron Status (n = 59)	*P*
Age	35 [31–42]	36 [32–44]	ns
Sex (n)			
Female/Male	39/6	35/24	0.01
CD/UC (n)	23/22	35/24	ns
Months since IBD diagnosis	120 [60–168]	140 [72–194]	ns
Montreal CD (n)			ns
Age at diagnosis			
A1: <16	3	7	
A2: 17–40	18	25	
A3: >40	2	3	
Location of disease (n)			ns
L1: ileal	13	15	
L2: colonic	3	3	
L3: ileocolonic	3	17	
L4: isolated upper GI	0	0	
L1 + L4	2	0	
L2 + L4	1	0	
L3 + L4	1	0	
Behavior of disease (n)			ns
B1: nonstricturing and nonpenetrating	7	14	
B2: stricturing	5	1	
B3: penetrating	3	7	
B1 + *P*[a]	6	8	
B2 + *P*[a]	2	5	
B3 + *P*[a]	0	2	
Montreal UC (n)			ns
Extension			
E1: proctitis	2	3	
E2: left sided	8	7	
E3: extensive	12	14	
Extraintestinal manifestations: n (%)	14 (31)	16 (27)	ns
Treatment of IBD: n (%)			ns
Salicylates	18 (40)	17 (29)	
Immunomodulators	20 (44)	33 (56)	
Biologics	30 (67)	48 (81)	
CRP (mg/dL)	0.3 [0.06–0.5]	0.13 [0.04–0.3]	0.05
Hemoglobin (g/dL)	12.8 [12.3–13.5]	13.9 [12.7–14.9]	0.05
Harvey–Bradshaw Index	0 [0–1]	0 [0–1]	ns
SCCAI	0 [0–1]	0 [0–1]	ns
IBDQ-36 (global)	219 [169–235]	230 [211–238]	ns
Restoration of health (IBDQ-36 score >209): n (%)	25 (55)	46 (78)	0.05
Daily Fatigue Impact Scale	8 [3–17]	3 [0–8]	0.05

[a]*P* is added to B1–B3 when concomitant perianal disease is present.
CRP, C-reactive protein; ns, not significant; SCCAI, Simple Clinical Colitis Activity Index.

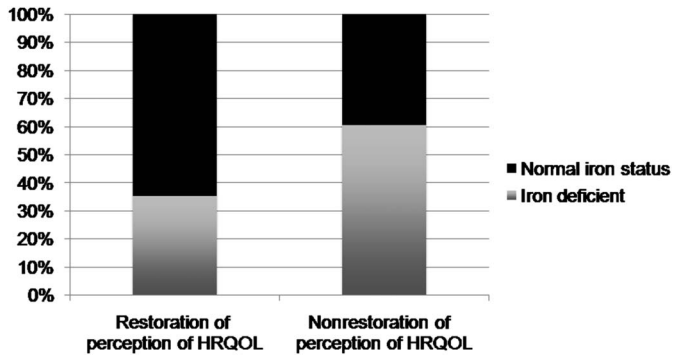

FIGURE 1. Restoration of perception of health between iron-deficient and normal iron status groups. *$P < 0.5$.

There are some limitations to our study; we used measures of iron stores (serum ferritin and transferrin saturation) to assess iron status. Although serum ferritin levels have been the mainstay to determine ID in most of the previous studies, there is no clear consensus on the optimal definition of iron status that provides clinically relevant information in a population with a chronic inflammatory disease. Also, because we evaluated activity based on clinical and biochemical indexes, we do not know whether subtle degrees of inflammation, relevant to HRQOL and iron metabolism, could potentially bias the result of our study.

Our definition of ID was very strict, as we only classified patients as iron deficient when they presented both low ferritin and transferrin saturation levels. Among the group of 59 patients who were classified as iron sufficient, all had ferritin levels more than or equal to 30 ng/mL.

Another limitation of our study is the low number of male patients with ID. Although this finding is expected, given the low incidence of ID in the general male population, it does not allow us to generalize our conclusions on the role that ID might play in the restoration of HRQOL in male patients with IBD.

In conclusion, our study suggests that ID in absence of anemia negatively impacts the normal perception of HRQOL patients with IBD in remission. Correction of ID may be a new target in the treatment of these patients.

TABLE 2. Clinical and Laboratory Data Distributed by HRQOL Restoration (Median and Interquartile Range)

	IBDQ-36 > 209	IBDQ-36 < 209	P
n = 104	71	33	
Iron status (n)			
Iron deficient	25	20	
Normal iron status	46	13	0.05
Sex (n): F/M	43/28	31/2	0.01
Hemoglobin (g/dL)	13.4 [12.6–14.5]	12.9 [12.5–14.0]	ns
Serum iron (μg/dL)	82.5 [58.5–115.7]	48 [33.5–72.0]	0.01
Ferritin (ng/mL)	29.5 [18.2–69.2]	20 [11.5–42.5]	0.05
Transferrin (mg/L)	266 [249–297]	277 [248–315]	ns
TfS%	33 [20.7–46]	15 [12.5–26.0]	0.01
CRP (mg/dL)	0.13 [0.04–0.30]	0.26 [0.15–0.49]	0.05

CRP, C-reactive protein; ns, not significant; Tfs, transferrin saturation.

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