Is iron deficiency in the absence of anemia associated with fatigue in inflammatory bowel disease?

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Abstract

Background: We aimed to determine if iron deficiency in the absence of anemia is associated with fatigue in inflammatory bowel disease (IBD).

Methods: 280 subjects in the population-based Manitoba IBD Cohort Study (Crohn's disease, (CD) 51%, ulcerative colitis (UC) 49%) had concurrent assessment of serum ferritin and hemoglobin, disease activity (Harvey Bradshaw Index for CD; Powell Tuck for UC), and fatigue (Multidimensional Fatigue Inventory (MFI). Iron deficiency was defined as ferritin <20 ug/L or a soluble transferrin receptor (sTfR) value>28 mg/L; anemia was defined as a serum hemoglobin value of < 140 g/L (males) and < 120 g/L (females). Problematic fatigue was defined as scoring > 95th percentile of a healthy sample on the General Fatigue scale of the MFI.

Results: Iron deficiency was identified in 20% (28/143) with CD and 27% (37/137) with UC. Anemia was identified overall in 50 (18%), with 230 who were nonanemic. In the nonanemic subgroup, there were no significant differences in mean fatigue levels (p values from 0.07 to 0.83 for fatigue subscales) or in proportions of those with problematic fatigue, comparing iron deficient (49%) and nondeficient groups (51%). Multivariate analyses indicated that there was no unique contribution of iron deficiency to problematic fatigue once active disease was adjusted for (OR 1.4, 95%CI 0.7-2.6).

Conclusion: There was no evidence of an association between iron deficiency and fatigue in the absence of anemia, suggesting that iron deficiency is not a clinically relevant contributor to fatigue in IBD.

Keywords: iron deficiency; anemia; Crohn’s disease; ulcerative colitis; fatigue

INTRODUCTION

Fatigue is a common concern of individuals suffering from chronic disease (1).Fatigue has been described extensively in cancer, multiple sclerosis, rheumatologic diseases, chronic kidney disease, and chronic liver disease, among others. (2-6). It is also quite prevalent in inflammatory bowel disease (IBD) (7-11) and has been shown to adversely affect quality of life (9). In population-based samples of individuals with IBD in Canada (8) and the Netherlands (9), problematic fatigue was reported by over two-thirds of those with active disease [70% (8); 76% (9)], and by 30% (8) and 37% (9) with inactive disease. Fatigue is not only one of the most common IBD symptoms reported, along with abdominal pain and diarrhea (7), it is also one of IBD patients' most predominant concerns (12).

Fatigue may result from a complex interaction of multiple factors including ongoing systemic inflammation, lack of restorative sleep, chronic pain, and psychological distress (6), all of which have been linked to fatigue in IBD (5,8). Anemia has often been assumed to be a primary causal factor of fatigue. .It has been reported to be strongly associated with fatigue in cancer (13, 14) as well as in IBD (9, 10, 15), although findings are not consistent (5). The anemia common to patients with IBD is mainly due to iron deficiency from blood loss, either alone or in combination, and suppression of erythropoiesis and iron binding (17, 18) due to pro-inflammatory cytokine activity. There has been support for aggressively treating anemia in IBD using iron therapy for those who are iron deficient and using erythropoietin for subjects with impaired red blood cell production (15, 18-20).

However, in the absence of anemia, it is unclear to what extent iron deficiency contributes to symptoms. Could iron deficiency itself be associated with fatigue? A recent systematic review of fatigue in IBD identified iron deficiency as a potential contributing factor to fatigue in IBD and emphasized the need for research to explore this finding (5). If it was determined that iron deficiency is in fact associated with patient-relevant symptoms such as fatigue, it would provide impetus for testing in clinical trials to determine the best course of intervention.

Previously, IBD research that assessed iron deficiency either didn't define it (21), used serum ferritin and mean corpuscular volume <66 (22), or used both serum ferritin and transferrin saturation (23) to estimate iron stores. Expert reviews have suggested the use primarily of serum ferritin (with or without transferrin saturation) (18-20), with some indicating that the addition of sTfR could enhance the ascertainment of iron deficiency in IBD, considering that serum ferritin is an acute phase reactant and thus can be difficult to interpret in the presence of inflammation (19, 20). Soluble transferrin receptor (sTfR) is thought to be more sensitive than ferritin at detecting iron deficiency, although the incremental utility of this index continues to be debated (24, 25). That is, the sTfR receptor is elevated in iron deficient states, but is significantly less affected by inflammation than typical iron indices (ferritin, serum iron and total iron binding capacity, and percent transferrin saturation) (24, 26, 27).

In this study, we aimed to investigate the relationship between iron deficiency and fatigue in IBD, in the absence of anemia. We hypothesized that those who were iron deficient would be more likely to experience significant fatigue than who were nondeficient, anticipating a more modest relationship overall between iron deficiency and fatigue than between anemia and

fatigue. We used a population-based IBD sample which included those with active and quiescent disease, and aimed to broaden and enhance the accuracy of identification of iron deficient individuals by utilizing a soluble transferrin receptor (sTfR) assay in addition to ferritin measurement.

MATERIALS AND METHODS

Participants

The Manitoba IBD Cohort Study was initiated in 2002, with participants who were at least 18 years old and diagnosed with IBD within the previous 7 years. They were recruited from a validated population-based research registry that has been previously described (28). The registry identifies and recruits subjects based on an administrative definition of IBD from the comprehensive health database of Manitoba Health, the single insurer that provides health care to all residents in the province. Of those eligible, that is all those with IBD in the province, just over half participate in the registry. This Cohort study was approved by the University of Manitoba Health Research Ethics Board and subjects provided written informed consent.

At the time of recruitment into the Cohort study, there were 3192 individuals in the research registry, of which 606 were eligible for this study, given the criteria regarding age and recent disease onset. Approximately 14% declined to take part, and another 17% could not be contacted. Complete data were obtained in the first contact from 388 of those enrolled, and they have subsequently served as the cohort, described elsewhere in detail (29). Population representativeness was assessed by comparing cohort participants to all other IBD cases diagnosed in the same time period, using a comprehensive validated data set which includes all

those in the province with IBD (the University of Manitoba IBD Epidemiology Database). Results indicated there were no significant differences on standard demographic comparisons including mean age, age distribution, sex distribution, urban versus rural residence, and mean duration of disease, suggesting excellent representativeness (30).

In the Cohort study, information on core clinical and psychological parameters is obtained every six months through survey, and annually through clinical interviews completed by research nurses. New variables or more detailed data collection are added annually. The data for the variables of interest in this study, which included fatigue, disease activity, and iron-related laboratory parameters were collected concurrently for each participant, 24 months after entry into the longitudinal study. At that point, there were 318 with diagnostic and current disease activity information actively participating in the Cohort. The variables assessed for this study were obtained through clinical interview, self-report survey, and blood samples.

Disease type and activity

The diagnosis and subtype of IBD were verified through chart review, which was completed by study staff at physicians' offices. Current disease activity was determined based on standardized clinical indices obtained during the clinical interview, using the Harvey-Bradshaw for Crohn's disease (CD) and the Powell-Tuck for ulcerative colitis (UC) (31, 32). Cut off levels of $\geq$5 were used to identify active IBD (33, 34).

Fatigue

Fatigue was assessed using a standardized, validated self-report measure. The Multidimensional Fatigue Inventory (MFI) is a 20-item self-report instrument designed to measure five aspects of current fatigue: General fatigue, Physical fatigue, Mental fatigue, Reduced Activity, and Reduced Motivation (16).The score on each subscale ranges from 4-20, with higher scores indicating greater fatigue. The General Fatigue subscale is commonly referenced as the primary fatigue descriptor, rather than a total MFI scale score. A cutoff of $\geq$ 13 for the General Fatigue subscale was used to delineate significant fatigue, as has been done in previous IBD studies based on the 95th percentile of the score in a healthy control group (9, 11, 35).

Anemia and Iron Deficiency

Anemia was defined as a serum hemoglobin value of less than 140 g/l in males and less than 120 g/l in females, as per usual lab parameters. In this study, iron deficiency was defined based on lab assay standards as serum ferritin <20 ug/L or a soluble transferrin receptor> 28 mg/L, the manufacturer's suggested cutoff, irrespective of ferritin level. Ferritin is known to reflect total body iron stores in states of health, but increases in response to inflammation (36). Measuring sTfR concentration can improve the diagnostic accuracy of iron deficiency, particularly in the setting of inflammation or chronic disease. sTfR is inversely related to intracellular iron stores, but is relatively insensitive to inflammation(22). Individuals were classified as either iron deficient (ferritin < 20 ug/L or sTfR> 28 mg/L) or iron nondeficient (ferritin $\geq$20 ug/L and sTfR$\leq$ 28 mg/L). Ferritin was measured by an immunoturbimetric assay (Roche Diagnostics, Laval, QC). The sTfRwas measured using a commercially available human sTfR ELISA Immunoassay (Quantikine IVD, R&D Systems, Minneapolis, Mn).

Statistical analysis

Hemoglobin and ferritin mean levels were compared between disease type and between disease activity status, using two-tailed t tests. Proportions with or without anemia and iron deficiency were also compared between disease types and between disease activity status using chi square tests. We then explored the relationship between iron deficiency and fatigue among the subset of those who were nonanemic. Mean levels of fatigue, considering different domains of fatigue, for the iron deficient and iron nondeficient groups were compared using 2 tailed t tests; Fisher's exact tests were used to compare proportions of those with significant fatigue with or without iron deficiency. Where necessary, a Bonferroni correction was used to correct for multiple comparisons. A secondary analysis using Fisher's exact test was conducted to compare proportions with high fatigue in two distinct ferritin groups to ensure there was no overlap: those with serum ferritin <20 (iron deficient) and those with serum ferritin ≥ 100 (iron replete). Finally, multivariate logistic regression was used to assess the relationship between fatigue and iron deficiency, adjusting for active disease, and anemia, in addition to potentially relevant demographic factors of sex and age.

RESULTS

Complete lab values were not available for 29 participants; an additional 9 had incomplete fatigue or disease activity data (see Figure 1). For the remaining 280, the mean age was 44 (SD =14.82), and the sample ranged from 19 to 85 years old. Disease duration was, on average, 6.3 years (SD = 2.1) at the time of this study. The sample was 62% female, and 90% were Caucasian, with a minority having self-described backgrounds as Metis (of Aboriginal and European ancestry), Hispanic or East Indian. One quarter of the sample reported having a university degree. Most respondents were in a partner relationship (married or common-law, 69%) and employed full- or part-time (68%). Fifty-one percent (143) had CD, and the remainder

(137) had UC. Forty-six percent (n=128) had current active disease, based on the Harvey Bradshaw or Powell Tuck clinical indices.

Eighteen percent overall were anemic, and 23% overall were iron deficient. There were no significant differences in mean hemoglobin, ferritin, or sTfR levels for those with CD or UC (Table 1). Comparing inactive to active disease, there were no significant differences in mean ferritin or sTfR levels. Those with active disease had lower mean hemoglobin levels than those with inactive disease, but the difference did not reach the significance threshold (Table 1; p=0.04). Considering total proportions with anemia or iron deficiency, there were no significant differences, comparing disease subtypes, or comparing active and inactive disease (Table 1).

Of the total sample, 14% were identified as nonanemic and iron deficient, and 68% had neither anemia nor iron deficiency. There were no significant differences between CD and UC or between those with active and inactive disease regarding proportions who were anemic with and without iron deficiency, or in proportions who were nonanemic with and without iron deficiency (Table 1).

The primary outcome of interest was the relationship of fatigue with iron levels, comparing those who were either iron deficient (n=50) or not iron deficient in the IBD subgroup of those without anemia (n=230). There were no mean differences in types of fatigue (e.g., physical, mental) or fatigue outcomes (e.g., reduced activity) between the iron deficient and iron nondeficient groups (Table 2). Further, while 49% with iron deficiency had problematic fatigue, a similar proportion without any iron deficiency also had problematic fatigue (45%) (Table 3). In addition, when

comparing the distinct ferritin subgroups(i.e., those with serum ferritin <20 vs those with serum ferritin ≥ 100), there was no significant difference in the proportions who had problematic fatigue (iron deficient 42% vs iron replete 58%; $p = 0.36$; data not shown in table).

Table 4 shows the bivariate and adjusted multivariate logistic regressions assessing the contributions of active disease, anemia and iron deficiency to fatigue, after controlling for age and sex. Problematic fatigue was almost seven times more likely to occur during active disease (OR 6.9, 95% CI 4.0-11.8). In the multivariate analysis, when controlling for age, sex, active disease and anemia, iron deficiency did not uniquely contribute to the likelihood of significant fatigue (adjusted OR1.1, 95% CI0.6-2.2).

DISCUSSION

In what we believe to be the first study to date exploring the relationship between iron deficiency and fatigue in non-anemic persons with IBD, we were not able to establish any relevant association between iron deficiency and fatigue. Two previous IBD-related studies reported that anemia was associated with fatigue, although they had not measured iron deficiency. Using the same fatigue measure as we did, a population-based Dutch study found that anemia correlated with fatigue in UC patients but not in CD(9), and in a single center Norwegian study, anemia was significantly associated with chronic fatigue (i.e., fatigue for at least 6 months measured by the Fatigue Questionnaire)(37). A report from Scandinavia, based on 425 outpatients, assessed both anemia and iron deficiency. Similar to our findings, they reported 44% of all subjects were fatigued, while 19% were anemic, and 34% were iron deficient. This study used a more liberal definition than our study (ferritin <30 ug/L). Anemia was not associated with fatigue and neither

was iron deficiency, although the investigators did not distinguish the role of iron deficiency in the absence of anemia (11).

The issue as to whether iron deficiency in the absence of anemia, or even anemia itself, has negative sequelae related to fatigue or other cognitive processes has been the focus of some randomized controlled studies, dating back as far as 1960 (38-40), with inconclusive results. Older reviews argued that iron deficiency was important in childhood cognitive development and adult exercise tolerance (41, 42). While the authors made the case that iron deficiency anemia was clearly detrimental, it was not established whether iron deficiency in the absence of anemia was detrimental. More recent findings from controlled studies in healthy women have suggested a link between iron deficiency and fatigue (43-46) or learning and memory (47).

These studies collectively indicate a relationship between iron deficiency and fatigue in healthy women, and suggest a role for iron in fatigue reduction, at least in the environment of a depleted iron state. However, in the context of IBD, the relationship between iron deficiency and fatigue was not evident in our study. Perhaps in the presence of chronic disease, whether active or in remission, other processes related to stress or sleep disturbances may play a greater contributory role with fatigue in IBD than measurable iron levels (8). It should be noted that iron sequestration, and thus possibly iron deficiency in the setting of prolonged chronic illness, is a genetic determined adaptive response to sickness (48). The mechanism of iron deficiency in IBD patients and subsequent response to iron supplementation may therefore be fundamentally different than iron deficiency seen in healthy women. Though speculative, given the role of iron to the generation of hydroxyl free radical and unstable oxygen species via the Fenton reaction

(49), iron sequestration may represent an appropriate adaptation to chronic illness, and thus obscure the relationship of iron deficiency and fatigue observed in other contexts.

This study used a population-based rather than clinic IBD sample, which has the advantage of greater generalizability to the range of experience for those living with IBD. However, since the rates of anemia we found were lower than what has been reported in clinical IBD samples, it is possible there was insufficient power to detect a significant relationship. In addition, we used measures of iron stores (serum ferritin) as well as soluble transferring receptor, to more comprehensively assess iron status. While serum ferritin levels are the mainstay to determine iron deficiency in most of the previous studies in healthy women, 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. It is certainly possible that measurement of iron stores is not accurate or precise enough to delineate a potentially subtle relationship between iron deficiency and fatigue. Since there is some uncertainty about the utility of sTfR, we also assessed the fatigue and iron deficiency relationships by comparing those more highly likely to be iron deficient (serum ferritin<20 ug/L) and those more highly likely to be iron replete (serum ferritin >100 ug/L) and there was still no difference in significant fatigue in those groups. Finally, while disease activity was assessed through available clinical indices, the potential that subtle degrees of inflammation, both relevant to iron metabolism or fatigue, might bias the result of this study (differentially or towards the null), is unknown but cannot be excluded.

In conclusion, our data suggest that, at least for persons with IBD, iron deficiency in the absence of anemia does not correlate with clinically relevant fatigue. Clinical trials designed to assess the

efficacy and safety of iron supplementation for the treatment of fatigue in this patient population are needed before this therapeutic strategy can be endorsed.

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Table 1: Anemia and Iron deficiency in Crohn's disease (CD) and ulcerative colitis (UC) participants with active and inactive disease

	CD		UC		Statistical comparison	
	Active Mean (SD)	Inactive Mean (SD)	Active Mean (SD)	Inactive Mean (SD)	Disease type[a]	Disease Activity[b]
N	68	75	60	77		
Hemoglobin level (g/L)	136.0 (12)	136.2 (13)	132.9 (15)	139.6 (15)	p=0.74	p=0.04
Ferritin level (ug/L)	89.3 (79)	65.5 (71)	86.1 (107)	85.5 (68)	p=0.35	p=0.21
sTfR level	18.6 (6)	19.0 (6)	21.3 (8)	19.3 (7)	p=0.09	p=0.42
Classification:	% (n)	% (n)	% (n)	% (n)		
Total Anemic	19 (13)	20 (15)	25 (15)	9 (7)	p=0.44	p=0.11
Total Iron deficient (ferritin< 20 ug/L or sTfR> 28)	18 (12)	21 (16)	30 (18)	25 (19)	p=0.14	p=0.94
SubClassifications:						
Anemic & iron deficient	7 (5)	11 (8)	15 (9)	5 (4)	p=1.0	p=0.85
Anemic & iron nondeficient	12 (8)	9 (7)	10 (6)	4 (3)	p=0.31	p=0.54
Nonanemic & iron deficient	10 (7)	11 (8)	15 (9)	20 (15)	p=0.56	p=0.11
Normal: nonanemic & iron nondeficient	71 (48)	69 (52)	60 (36)	71 (55)	p=0.20	p=0.34

[a]comparisons between CD and UC, collapsing across disease activity; [b]comparisons between active and inactive disease, collapsing across CD/UC; comparisons are based on t-test and Chi-square test where applicable; Bonferrroni correction ($p \leq 0.02$).

Table 2.Mean fatigue levels comparing those with and without iron deficiency, for the nonanemic subgroup (n=230)

	Iron Deficient	Iron Nondeficient		
	Mean (SD)	Mean (SD)	t-value	P value
Multidimensional Fatigue Inventory				
General Fatigue	12.0 (4.9)	11.7 (4.5)	0.34	0.73
Physical Fatigue	8.8 (3.6)	9.4 (4.0)	-0.86	0.39
Mental Fatigue	9.4 (4.2)	8.1 (3.5)	1.88	0.07
Reduced Activity	8.6 (3.7)	8.5 (3.6)	0.22	0.83
Reduced Motivation	7.6 (3.2)	7.9 (3.5)	-0.57	0.57

Table 3. Comparisons of fatigue and iron status for the nonanemic subgroup (n=230)

	High Fatigue (≥13 on MFI)	Not Fatigued (<13 on MFI)
Iron Deficient (ferritin<20 ug/L or sTfR>28)	49% (19/39)	51% (20/39)
Iron nondeficient (ferritin ≥20ug/L + sTfR≤28)	45% (86/191)	55% (105/191)

Chi-square = 0.67, Fisher's exact test p = 0.73

Table 4. Relationship between fatigue levels and disease activity, anemia and iron deficiency, controlling for age and sex

	High Fatigue %	Not fatigued %	Bivariate logistic regression Odds ratio (95% CI)	Multivariate logistic regression Adjusted OR (95% CI)
Active disease	71	29	6.9 (4.0-11.8)	6.8 (3.9-11.7)
Anemia	58	42	1.9 (1.0-3.5)	1.5 (0.7-3.2)
Iron deficiency	54	46	1.2 (0.7-2.2)	1.1 (0.6-2.2)

Figure 1 Flow diagram of participant classification regarding anemia and iron deficiency