

Iron Deficiency Is Common During Remission in Children With Inflammatory Bowel Disease

Global Pediatric Health
Volume 3: 1–5
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DOI: 10.1177/2333794X16633672
gph.sagepub.com
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Abstract

The aim was to study prevalence of iron deficiency in children with inflammatory bowel disease (IBD) during remission. In addition, there was an observational evaluation of hematological response to oral iron. A population-based retrospective study including 90 Swedish children (median 13 years) with IBD was performed. Patient records covered in median 25 months. Iron deficiency was present in 70/77 children (91%) in which iron status could be assessed. In clinical and biochemical remission, iron deficiency was found in 57/67 (85%) of children, and 23 (34%) of them had iron deficiency anemia. Thirty-six iron-deficient children were prescribed oral iron supplementation and 32 (89%) improved hemoglobin levels over 6 months. In conclusion, iron deficiency is common during clinical remission in children with IBD, even in cohorts with low prevalence of anemia. Therefore, regular biochemical screening for iron deficiency is warranted during all stages of disease, irrespective of symptoms and inflammatory blood markers.

Keywords

anemia, children, inflammatory bowel disease, iron deficiency, iron supplementation

Received January 6, 2016. Received revised January 6, 2016. Accepted for publication January 12, 2015

Introduction

Inflammatory bowel disease (IBD) includes Crohn disease (CD), ulcerative colitis (UC), and “inflammatory bowel disease, type unclassified.” Anemia is common in children with IBD with a reported prevalence of 41% to 74%.^{1–4} Iron deficiency is the most frequent reason for anemia in adult IBD patients.^{5,6} Data are scarce in children although 2 retrospective British studies recently reported iron deficiency among 60% to 80% of children and adolescents with IBD.^{1,2} Iron deficiency anemia in adults has a significant impact on quality of life (QoL).^{7,8} Even without anemia, iron deficiency is associated with fatigue, headache, and dizziness and may reduce cognitive and physical performance.^{9,10}

Disease activity is considered to be the key determinant of anemia in adult IBD patients.^{2,11} Nevertheless, 65% of patients with anemia in a population-based adult study were reported to be in clinical remission.⁵ The prevalence of iron deficiency and anemia during remission in pediatric IBD cohorts is less studied.

It may be difficult to identify iron deficiency anemia in patients with IBD. Most biochemical markers of iron

deficiency, including serum ferritin, are acute-phase reactants and must therefore be interpreted in relation to the activity of the intestinal inflammation.^{12–14} The focus of IBD anemia management has long been on controlling disease activity while awaiting spontaneous hematological recovery, rather than iron treatment. One reason is that oral iron supplementation is considered to be inefficient and associated with frequent side effects, possibly including aggravation of intestinal inflammation.¹⁵ More recently, intravenous iron formulae with good tolerability at higher doses have been developed, capable of normalizing iron deficiency and anemia in spite of remaining inflammatory activity.¹⁶ With improved treatment options, interest in iron deficiency in IBD has increased.

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The aim of this study was to assess the prevalence of iron deficiency and iron deficiency anemia in a population-based cohort of Swedish children with IBD, specifically during periods of remission, and to evaluate the response to oral iron supplementation in children with IBD-associated iron deficiency anemia.

Methods

Study Group and Population

We conducted a population-based retrospective study in the County of Värmland, Sweden (total population of 53 300 children). All children (0-18 years) diagnosed with IBD in the county are referred to the Department of Pediatrics at Karlstad Central Hospital where the study was performed. We included children visiting our clinic due to a previous or new diagnosis of IBD during the study period from April 2007 to December 2011. The same diagnostic criteria (including endoscopic, histological, and radiographic findings) were used as in previous IBD incidence studies in Sweden.^{17,18} Patients were included if patient records during the study period covered at least one pre-scheduled follow-up visit in clinical and biochemical remission (defined as absence of intestinal symptoms and normal C-reactive protein [CRP; <10 mg/L] or erythrocyte sedimentation rate [ESR; <10]). Normally follow-up visits were scheduled every 6 months. Patients were followed until 18 years of age or to the end of the study period.

Study Data

All study data including blood tests were obtained from the electronic patient records: sex, age, age at diagnosis, medication, levels of hemoglobin, mean corpuscular volume, ESR, CRP, serum iron, total iron binding capacity, transferrin saturation, and serum ferritin. We also determined whether any symptoms of IBD were reported at clinical follow-up visits adjacent to blood sampling.

Anemia was defined according to the age adjusted World Health Organization criteria,¹⁹ and iron deficiency was defined as previously recommended¹⁴: in remission (CRP <10 mg/L), ferritin <30 µg/L, or transferrin saturation <16%; in active disease (CRP >10 mg/L), ferritin <100 µg/L, and transferrin saturation <20%. In 2 patients without available iron status, anemia was present with microcytosis during remission and iron deficiency was then assumed as previously suggested.^{6,20} Change in hemoglobin from initiation of iron supplementation to laboratory follow-up 6 months later was assessed in patients treated with iron.

Nonparametric statistics (Mann-Whitney *U* test, Wilcoxon signed rank test, and Fisher's exact as

appropriate) were applied, and all calculations were performed in SPSS (Version 20, IBM, New York, NY).

Results

Overall Prevalence of Iron Deficiency and Anemia

Ninety-four children were identified visiting the clinic due to IBD during the study period. Of these, 90 had at least one follow-up visit in remission within the study period and constitute the study cohort. Descriptive data of the cohort are presented in Table 1, and data on prevalence of iron deficiency and anemia are presented in Figure 1.

Forty-six of the patients had their IBD diagnosis during the study period, and at presentation 21 of them (46%) were anemic. In routine care iron status was not evaluated at diagnostic examinations.

Iron Deficiency and Anemia During Remission

Iron status at the first follow-up visit in remission within the study period was assessed in 67 (74%) of the 90 patients. Out of these patients 57 (85%) met the criteria of iron deficiency and 23 (34%) were considered to have simultaneous iron deficiency anemia. Among the remaining 23 patients without iron status analyzed at follow-up visit in remission, 7 children had anemia of therefore unknown origin.

There were no differences in iron deficiency or anemia prevalence depending on specific IBD diagnosis (Table 2) or according to sex. Furthermore, there were no associations between iron deficiency or anemia and the duration of disease since diagnosis, or age.

Iron Supplementation

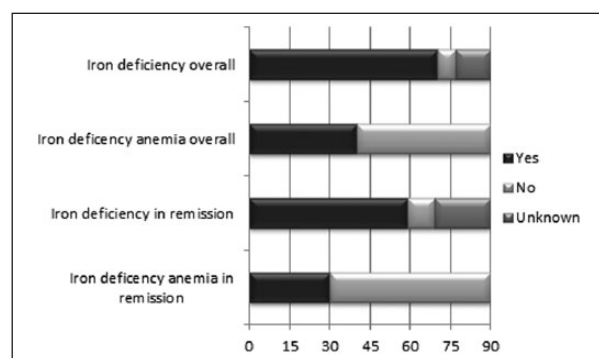
During the entire study period, 36 iron-deficient children (27 with iron deficiency anemia) were prescribed oral iron supplementation (ferrous glycine sulfate 100 mg daily or ferrous succinate 200-400 mg daily), normally during 3 months. Six months after iron prescription, hemoglobin levels had increased in 32 (89%) and normalized in 16 (59%) of the 27 anemic patients. Median (range) hemoglobin prior to treatment was 109 (76-142) g/L and after oral iron supplementation 125 (107-151) g/L ($P < .001$). Another 4 iron-deficient children received a combination of oral and intravenous iron, and 3 children received intravenous iron only (all were anemic before initiation of intravenous substitution; none were anemic 6 months later).

Table 1. Basal Data on the 90 Children in the Study Group^a.

Basal Descriptive Data		Medication During Study Period	n
CD/UC/IBDU (n)	28/45/17	5-ASA monotherapy	38
Male/female (n)	43/47	Combination including AZA or MTX	37
Age at diagnosis (years)	13 (10-15)	Combination including anti-TNF	8
Duration from diagnosis to first visit within the study period (months)	13 (8-36)	Combination including surgery	7
Study duration included (months)	26 (14-38)		

Abbreviations: CD, Crohn disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease, type unclassified; 5-ASA, aminosalicylate; AZA, azathioprine; MTX, methotrexate; anti-TNF, anti-tumor necrosis factor.

^aValues are presented as median (interquartile range).

**Figure 1.** Iron deficiency and anemia in the cohort.

Of the 90 patients, 70 (78%) met criteria of iron deficiency during the study period. This corresponds to a period prevalence of 78% in the total study group and of 91% in the 77 children whose iron status was ever analyzed during the study period. Forty (44%) of the 90 patients met criteria of anemia during the study period. At first follow-up visit in remission, 57 patients (63%) met criteria of iron deficiency, and 30 patients (33%) were considered anemic.

Discussion

In this population-based pediatric IBD study we report that 85% of the patients whose iron status were analyzed in remission met criteria of iron deficiency. If one were strictly to assume that no patient without an iron status had a deficiency, 63% of the total cohort would still have an iron deficiency at first visit in remission. We also found a 91% period prevalence of iron deficiency in pre-scheduled clinical follow-up visits (over a median time of 26 months) among the children whose iron status was ever analyzed during the study period.

Previous studies report a broad anemia prevalence range in pediatric IBD, likely reflecting methodological differences,¹⁻⁴ and extrapolation to other populations have been questioned.² The figures on iron deficiency in our cohort are however consistent with previous retrospective British pediatric IBD studies,^{1,2} despite the much lower frequency of anemia at diagnosis observed in our cohort.

Goodhand et al showed considerable difference in anemia occurrence in relation to age (70% of children and 42% of adolescents were anemic).² We found no such correlation, nor any correlation between age and iron deficiency. In addition, we found no association between type of IBD and anemia or iron deficiency. This is consistent with the findings of Wiskin et al¹ and a recent Swedish study where anemia was more common among patients with CD compared with UC at diagnosis but with no difference between the groups at follow-up 1 year later,¹¹ however in discrepancy with another Scandinavian adult IBD study where anemia was significantly more common in CD than UC patients.⁶

In our cohort, 48% of all children (73% of children who met criteria of iron deficiency) were prescribed iron supplementation, compared with 16%¹ and 20% of iron-deficient patients,² respectively, in the 2 British pediatric IBD studies. In our study, 89% of the patients increased their hemoglobin levels during oral treatment. Lack of a control group and adherence assessments for the data on iron substitution mean that no robust conclusions on efficacy can be made. Spontaneous hematological recovery is however known to be slow,²¹ and the observational study settings still indicate feasibility of oral iron substitution when tolerated. Iron supplementation in pediatric IBD populations is a controversial topic. The lower efficacy of oral iron substitution therapy, demonstrated in several comparative studies on adult IBD patients and the potential risk that enteral distribution of iron could induce or maintain intestinal mucosal inflammation,²² have guided the recently developed recommendations for adult IBD patients, stating that intravenous iron supplementation should be used if available.²³ Although one fifth of IBD patients are diagnosed during childhood or adolescence and the incidence of pediatric IBD is increasing worldwide, none of the modern intravenous iron formulas have yet been approved for treatment of children.²⁴ Also, data on effect and tolerance of oral iron in children with IBD are scarce, and in contrast to studies in adult IBD patients

Table 2. Period and Point Prevalence of Iron Deficiency^a.

	CD	UC	IBDU	P Value
Iron deficiency during study period	25/27 (93%)	35/40 (88%)	10/10 (100%)	NS
Iron deficiency at first follow-up	22/24 (92%)	28/34 (82%)	7/9 (78%)	NS

Abbreviations: CD, Crohn disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease, type unclassified; NS, not significant.

^aData are prevalence during the study period and at first follow-up visit in remission, respectively, in children with available iron status. Groups according to specific IBD diagnosis and *P* value for difference between groups.

there are no data showing that iron supplementation improves QoL in children.⁸

The present study has limitations due to the retrospective population-based design, this also being one of its strengths by avoiding selection bias. Laboratory data were not evenly available in all patients. Therefore, there might be a risk of bias due to relative overinclusion of patients with active and still suboptimally treated disease since they are more likely to have laboratory tests performed. However, we identified a high prevalence of iron deficiency during clinical and biochemical remission, and interestingly a much higher prevalence of iron deficiency relative to anemia. Using the first appointment during remission within the study period for assessment of iron status may in some cases mean that the duration of remission is not sufficient for restitution of iron storages. It must though be pointed out that half of the cohort already had a IBD diagnosis previous to the study period, most patients were not anemic (suggesting that nutritional status was sufficient for erythropoiesis and indicating stable remission), and we recognized no association between the duration of disease and iron deficiency. We are aware that CRP and ESR may be normal despite residual disease activity, but due to the retrospective design no standardized endoscopic assessments were available during clinical remission. For practical reasons a later sampling point for iron status could not be used in this design since a majority of children were prescribed supplementation after the first identification of iron deficiency anemia. Despite limitations our study indicates that iron deficiency is common also during remission in children with IBD. This implies that regular biochemical screening, not only for anemia as previously proposed,²³ but also for iron deficiency is warranted in this population.

Together with previous work, it could be regarded as established that iron deficiency and iron deficiency anemia is common in children with IBD, but larger samples will be needed to identify subgroups of pediatric IBD (eg, regarding age or diagnosis) at highest risk of iron deficiency. In future studies the consequences of, especially, nonanemic iron deficiency need to be studied, since unnecessary iron treatment should be avoided. For

the same reasons the importance of remission duration should be further studied even though we could not identify this as a determinant of iron deficiency prevalence. Randomized controlled trials for the comparison of tolerability, efficacy, and QoL aspects of intravenous versus oral iron in pediatric populations are also needed.

In conclusion, iron deficiency is common during clinical remission in children with IBD, even in cohorts with a relatively low prevalence of anemia. Therefore, regular biochemical screening for iron deficiency is warranted in this population, during all stages of disease, irrespective of symptoms and inflammatory blood markers.

Acknowledgments

The investigators thank the patients and their parents; the Department of Pediatrics, Karlstad Central Hospital, for help with data collection; and the Center for Clinical Research, County Council of Värmland, Sweden, for helpful advice.

Author Contributions

EW, PM, CAH and SW contributed to study design. EW, MF and SW contributed to acquisition of data and EW and SW to analysis of data. All authors contributed to interpretation of data and writing of the manuscript.

Authors' Note

The research protocol was approved by the Regional Research Ethics Board at Uppsala University (Registration No. 2013/208) with the judgment that (in line with the population-based retrospective design using already present clinical data) no individual formal consent was requested to fulfill ethical standards.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: EW was supported by the County Council

of Värmland, Sweden and SW was supported by Örebro University, Sweden.

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