

Anemija pri otrocih in mladostnikih s kronično vnetno črevesno boleznijo ob diagnozi ter po enem letu zdravljenja

Anemia in children and adolescents with inflammatory bowel disease at the time of diagnosis and after 1 year of treatment

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Izvleček

Namen: Anemija je najpogostejši sistemski zaplet kronične vnetne črevesne bolezni (KVČB). Glede na diagnostične kriterije je lahko prevalenca anemije tudi 73,7 %. Podatki nakazujejo, da je prevalenca anemije višja v pediatrični kot odrasli populaciji pacientov. Anemija lahko pomembno vpliva na pacientovo kvaliteto življenja, le-ta je lahko tako nizka kot pri bolnikih z napredovalim rakom. Kvaliteta življenja pa se izboljša z zvišanjem hemoglobina. Ker je anemija pogosto neprepoznana in nezdravljena, je ta potencialno reverzibilen zaplet cilj naše raziskave.

Metode: Zbrali smo podatke 44 otrok, starih od 10 do 18 let (povprečna starost 14,3 leta, 25 fantov, 19 deklet), iz časa diagnoze ter podatke iz obdobja po enem letu od zdravljenja zaradi KVČB ter jih primerjali s 36 zdravimi otroki, stari od 10 do 18 let (povprečna starost 13,7 let, 17 fantov, 19 deklet). Izračunali smo prevalenco anemije (z merili SZO) ter

Abstract

Purpose: Purpose: Anemia is the most common systemic complication of inflammatory bowel disease (IBD). Depending on the diagnostic criteria and patient sub-population, the prevalence of anemia can be as high as 73.7%. Data suggest that the prevalence of anemia is often higher in the pediatric population than adults. The presence of anemia can have a significant impact on the quality of life (QOL) in patients with IBD, which can be as poor as exists in patients with advanced cancer; however, the QOL improves with restoration of the hemoglobin concentration. Because the anemia in patients with IBD is often unrecognized and/or undertreated, this potentially reversible condition is an area of great concern.

Methods: We retrospectively collected data for 44 pediatric patients (age range, 10–18 years; mean age, 14.3 years; 25 boys and 19 girls) at the time of diagnosis and after 1 year of IBD treatment and compared the

izmerili nivoje hemoglobina, železa, feritina ter volumen eritrocitov (MCV). Medsebojno smo primerjali tudi KVČB bolnike glede na to, ali so bili zdravljeni tudi zaradi anemije.

Rezultati: Anemija je bila prisotna pri 63 % pacientov KVČB v času diagnoze, pri istih pacientih po enem letu v 18 % ter v kontrolni skupini pri 3 %. Krvni parametri so se v enem letu zdravljenja za osnovno bolezen izboljšali ter približali vrednostim kontrolne skupine. 20 % KVČB pacientov je bilo zdravljenih tudi za anemijo. Med KVČB pacienti, ki so bili zdravljeni tudi za anemijo, ter tistimi, ki niso bili, nismo našli statistično pomembne razlike.

Zaključek: Rezultati namigujejo, da se anemija izboljša že samo z zdravljenjem osnovne bolezni. Hkrati pa smo odkrili tudi precej majhen delež bolnikov, zdravljenih za anemijo, kar bi bilo treba dodatno preučiti.

IBD patients to 36 healthy children and adolescents (age range, 10–18 years; mean age, 13.7 years; 17 boys and 19 girls). We recorded the prevalence of anemia based on the World Health Organization criteria, the hemoglobin concentration, mean corpuscular volume, and iron and ferritin levels. We also compared IBD patients who were treated for anemia to untreated IBD patients.

Results: Anemia existed in 63% and 18% of IBD patients at the time of diagnosis and 1 year after treatment, respectively, and in 3% of the patients in the control group. Blood parameters in IBD patients improved after 1 year of treatment and approached the values in the control group. Of the IBD patients, 20% were treated for anemia. No statistical significance existed between IBD patients who were and were not treated for anemia.

Conclusion: Our findings suggest that anemia may improve in patients with IBD by treating the underlying disease; however, we also found a small percentage of patients who were treated for anemia, which is an issue that must be kept in mind.

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by severe inflammation of the small bowel and/or colon leading to recurrent diarrhea and persistent abdominal pain. Crohn's disease and ulcerative colitis are the two main clinicopathologic sub-types of IBD; indeterminate colitis is a rare third sub-type (1). The respective etiologies of Crohn's disease and ulcerative colitis are poorly understood, and both disorders are characterized by unpredictable exacerbations and remissions (2). Crohn's disease involves chronic inflammation of the alimentary system, anywhere from the mouth to the anus. The inflammatory process in Crohn's disease tends to be segmented and is often transmural (1). The manifestations of Crohn's disease include symptoms of inflammation (diarrhea, bleeding, and cramping), gastrointestinal obstruction, systemic symptoms (fever, malaise, and easy fatigability), and extraintestinal symptoms (anemia, arthritis, and

uveitis; 2). In contrast, ulcerative colitis involves chronic inflammation, which is restricted to the colon and spares the upper gastrointestinal tract. Ulcerative colitis usually begins in the rectum and extends proximally. Patients with ulcerative colitis typically present with bloody diarrhea (often nocturnal and postprandial), passage of pus, mucus, or both, and abdominal cramping during bowel movements (3). Definitive treatment for IBD is not available; thus, treatment is aimed at controlling symptoms and reducing the risk of recurrence. Patients undergoing treatment for IBD can be categorized as follows: first-line drugs (aminosalicylates); and corticosteroids, immunomodulators (azathioprine and 6-mercaptopurine), or monoclonal antibodies (infliximab). Surgical treatment is performed for intractable disease, complications of therapy, and fulminant disease that is unresponsive to medical management (2).

A common misconception is that anemia is a rare or clinically insignificant manifestation of IBD (4, 5); however, anemia is the most common extra-intestinal complication of IBD (5–7). Depending on the diagnostic criteria and patient age, the prevalence of anemia in patients with IBD can be as high as 73.7 % (8, 9). Data suggest that the prevalence of anemia is often higher in the pediatric population than adults (8–10). Anemia presents with a variety of symptoms, such as fatigue, headache, dizziness, shortness of breath, and tachycardia (7). Gastrointestinal motility disorders, nausea, anorexia, and malabsorption have all been attributed to anemia in patients with IBD (7). Anemia may also contribute to poor growth (11). Anemia in patients with IBD is of multi-factorial origin, and is frequently the result of a combination of iron deficiency and anemia of chronic disease (12). As in previous studies (10, 13–16), iron deficiency anemia is the most common cause of anemia in IBD patients and is a result of dietary restrictions, malabsorption (due to inflammation and/or resection of intestine), or intestinal bleeding (17, 18). In patients with active IBD, cytokines or hepcidin may reduce iron absorption, retain iron within cells of the reticular-endothelial system, and inhibit erythropoiesis (18, 19). Hence, anemia of chronic disease is also common in IBD patients (10, 20).

Other factors that contribute to the presentation of anemia include vitamin B12 malabsorption (in the terminal ileum and gastric Crohn's disease) and folate deficiency (malabsorption, inadequate diet, and side effects of sulfasalazine and methotrexate; 6). Direct myelosuppressive effects have also been reported for azathioprine/6-mercaptopurine and sometimes for sulfasalazine and 5-aminosalicylic acid (7, 21).

Considering the burden of menstrual blood loss, female patients are at even greater risk for developing anemia. Approximately three-quarters of adolescent females do not meet dietary iron requirements, compared to 17% of males (22). Additionally, various reports have pointed out a lower iron intake in patients with IBD (especially women), which

is predominantly due to avoidance of high fiber-fortified breakfast cereals and may be perceived to exacerbate abdominal symptoms (17).

The presence of anemia can have a significant impact on the quality of life (QOL) in patients with IBD, which can be as poor as patients with advanced cancer (4); however, the QOL often improves with restoration of a normal hemoglobin concentration (13, 23, 24). Because anemia in patients with IBD is often unrecognized and/or undertreated, this potentially reversible condition is an area of great concern (5, 10).

Despite being a common manifestation of IBD, data regarding the prevalence of anemia in pediatric patients with IBD are limited. For that reason, the aim of the current study was to determine the prevalence of anemia in IBD patients and to determine the efficacy of treatment 1 year after diagnosis.

MATERIAL AND METHODS

In this retrospective study, patient records were collected for 44 patients (age range, 10–18 years; mean age, 14.3 years; 25 boys and 19 girls) who were diagnosed with IBD. Laboratory values for blood hemoglobin concentration, mean corpuscular volume (MCV) of erythrocytes, and serum ferritin, iron, and C-reactive protein (CRP) levels were collected at the time of IBD diagnosis and 1 year later (mean disease duration collection time, 11.8 months; range, 11–13 months). The IBD group consisted of 23 patients with Crohn's disease (13 boys and ten girls), 20 patients with ulcerative colitis (11 boys and nine girls), and one boy with indeterminate colitis. The patients with IBD were diagnosed and treated according to existing guidelines (25–27). Additionally, nine of 44 IBD patients were treated for anemia (oral iron at a standard dose [n=2], intravenous iron at a standard dose [n=4], and iron-rich dietary supplementation [n=3, Ensure; Abbott, North Chicago, IL, USA]). Patients who stopped taking oral iron for any reason were considered “not treated with iron.”

In addition, 36 subjects (age range, 10–18 years; mean age, 13.7 years; 17 boys and 19 girls,) were selected as the control group, which consisted of children and adolescents who had no symptoms of IBD and who came to the Pediatric Clinic for evaluation after hospital discharge for various medical conditions, such as pneumonia, urinary tract infection, otitis media, and diarrhea. During the clinic visits, the parents and children or adolescents received information regarding the study. After obtaining written consent, the patients were enrolled in the study. The same laboratory parameters were obtained from the subjects in the control group. The study was approved by the Slovene National Medical Ethics Committee.

A comparison was made between patients who received treatment for anemia (oral or intravenous iron, or dietary supplementation) and patients who received no treatment. We compared the prevalence of anemia and hemoglobin concentration, MCV, and iron and ferritin levels between the two groups. Laboratory studies were performed in the Department of Laboratory Diagnostics of the University Medical Centre (Maribor, Slovenia). The hemoglobin concentration, MCV, and serum ferritin, iron, and CRP levels were determined in all of the patients with IBD and controls using standard methods. Anemia was defined according to World Health Organization criteria as follows: children 5–11 years of age, Hb < 115 g/L; children 12–14 years of age, Hb < 120 g/L; non-pregnant women, Hb < 120 g/L; and men, Hb < 130 g/L (28). We then divided the subjects into five groups based on the WHO criteria for anemia: males 10–11 years of age, Hb < 115 g/L; males 12–14 years of age, Hb < 120 g/L; males 15–18 years of age, Hb < 130 g/L; females 10–11 years of age, Hb < 115 g/L; and females 12–18 years of age, Hb < 120 g/L. The patient age range was 10–18 years and none of the females were pregnant.

Furthermore, ferritin values were included in the statistical analysis if the CRP level was < 10 mg/L because ferritin is an acute phase protein and elevated in inflammatory disorders.

Statistical analysis was performed with SPSS 20.0.0 for Windows. Descriptive statistics and analysis of variance (ANOVA) were used, as appropriate. All statistical values were considered significant at a P level < 0.01.

RESULTS

Difference in the prevalence of anemia and blood parameters between groups

At the time of IBD diagnosis, 63% of patients had anemia based on WHO criteria (Table 1). The prevalence in male and female patients was 48% and 84% at the time of diagnosis, respectively. After 1 year of treatment, the overall prevalence of anemia decreased to 18%. The prevalence of anemia in male and female patients after 1 year of treatment was 12% and 26%, respectively. One patient in the control group had anemia, which resulted in a prevalence of anemia in the control group of approximately 3% (Figure 1).

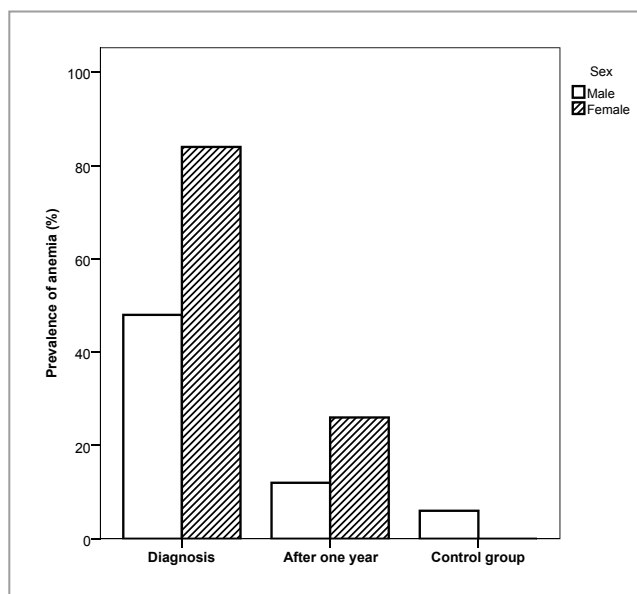


Figure 1. Prevalence of anemia. Figure shows the prevalence of anemia (in percentage points) at the time of diagnosis and after 1 year of treatment, and in the control group. Empty bars show the prevalence of anemia in males and the striped bars show the prevalence in females. The prevalence of anemia decreased markedly after 1 year of treatment in males and females; the prevalence of anemia in the control group was minimal.

Table 1. Prevalence of anemia and blood parameters

Parameter	Group	At the time of diagnosis	After 1 year of treatment	Control group	p ¹	p ²	p ³
Mean age [median]		14.3 [14]	15.3 [15]	13.7 [14]	0.05	0.251	0.003
Anemia prevalence	All	28/44 (63%)	8/44 (18%)	1/36 (3%)			
	Male	12/25 (48%)	3/25 (12%)	1/17 (6%)			
	Female	16/19 (84%)	5/19 (26%)	0/19 (0%)			
Mean hemoglobin (g/L)	Males 10-11*	113	120	135	§	0.001	§
	Males 12-14**	117	132	143	0.077	0.005	0.108
	Males 15-18***	130	145	144	0.029	0.256	0.875
	Females 10-11*	107	134	130	0.087	0.051	0.712
	Females 12-18**	109	125	132	<0.0001	<0.0001	0.029
Mean MCV (fl)	Male	77.5	82.7	81.3	0.008	0.057	0.361
	Female	77.1	82.6	85.1	0.032	<0.0001	0.219
Mean iron (µmol/L)	Male	6.5	12.2	17.5	0.004	<0.0001	0.037
	Female	7.5	12.3	16.3	0.05	<0.0001	0.081
Mean ferritin**** (µg/L) [N]	Male	35 [13]	26 [20]	40 [17]	0.324	0.478	0.077
	Female	30 [9]	18 [15]	31 [18]	0.322	0.683	0.916
* anemia is present at Hb < 115 g/L		P ¹ – p value comparing values at time of diagnosis and after 1 year of treatment					
** anemia is present at Hb < 120 g/L		P ² – p value comparing values at time of diagnosis and control group					
*** anemia is present at Hb < 130 g/L		P ³ – p value comparing values after 1 year of treatment and control group					
**** only cases with CRP < 10 mg/L		§ – one sub-group involved had less than three subjects					

Measurements of the hemoglobin concentration in the patients based on gender and age by WHO criteria showed results consistent with the overall prevalence of anemia (Table 1). Males 10–11 years of age had a mean hemoglobin concentration of 113 g/L at the time of diagnosis compared to 120 g/L after 1 year of treatment; the mean hemoglobin concentration in the control group was 135 g/L, and the difference between the IBD group at the time of diagnosis and the control group was statistically significant ($p = 0.001$; Figure 2). Males aged 12–14 years of age had a mean hemoglobin concentration of 117 g/L at the time of diagnosis compared to 132 g/L after 1 year of treatment; the mean hemoglobin concentration in the control group was 143 g/L in control group, and the difference between the IBD group at the time of diagnosis and control group was statistically significant ($p = 0.005$). Males 15–18 years of age had a mean hemoglobin concentration of 130 g/L at the time of diagnosis compared to 145 g/L after 1 year of treatment; the mean hemoglobin concentration in the control group was 144 g/L, and

the difference between the IBD group at the time of diagnosis and after 1 year of treatment was statistically significant ($p = 0.029$). Females 12–18 years of age had a mean hemoglobin concentration of 109 g/L at the time of diagnosis compared to 125 g/L after 1 year of treatment; the mean hemoglobin concentration in the control group was 132 g/L; the differences between these three subgroups were all statistically significant.

Measurements of the MCV yielded a similar distribution (Figure 3). Males at the time of IBD diagnosis had a mean MCV of 77.5 fl and the mean MCV was 82.7 fl after 1 year of treatment; the mean MCV in the control group was 81.3 fl, and a statistically significant difference existed between the patients with IBD at the time of diagnosis and after 1 year of treatment ($p = 0.008$). Female IBD patients had a mean MCV of 77.1 fl at the time of diagnosis and 82.6 fl after 1 year of treatment; the mean MVC in the control group was 85.1 fl, and a statistically significant difference existed between the MVC at the time of

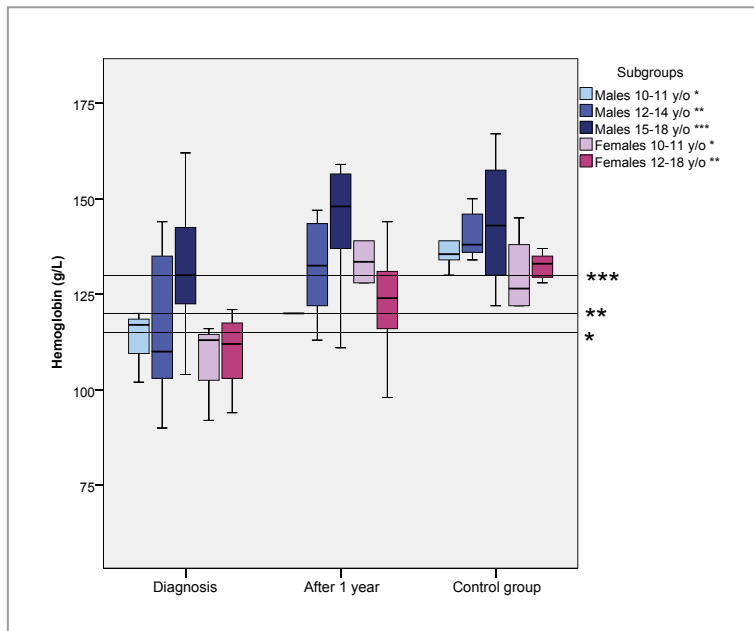


Figure 2. Hemoglobin levels in different groups. Figure represents the hemoglobin concentrations in different subgroups at the time of diagnosis and after 1 year of treatment, and in the control group. The hemoglobin concentrations in the IBD patients rise after 1 year of treatment approached the values of the control group. Three reference lines represent cut-off values of the hemoglobin concentration for the patient to be considered anemic. After 1 year of treatment, the mean hemoglobin concentration rose over the reference values of hemoglobin.

* - cut-off value of hemoglobin concentration in male children > 14 years of age (130 g/L)

** - cut-off value of hemoglobin concentration in children 12–14 years of age and in non-pregnant women > 14 years of age (120 g/L)

*** - cut-off value of hemoglobin concentration in children 5–11 years of age (115 g/L)

diagnosis and after 1 year of treatment ($p = 0.032$), and between the MVC at the time of diagnosis and the control group ($p < 0.0001$).

We also found lower values of serum iron between the three groups (Figure 4). Male patients with IBD had a mean iron level of $6.5 \mu\text{mol/L}$ at the time of diagnosis and $12.2 \mu\text{mol/L}$ after 1 year of treatment; males in the control group had a mean iron level of $17.5 \mu\text{mol/L}$. Female patients with IBD had a mean iron level of $7.5 \mu\text{mol/L}$ at the time of diagnosis and $12.3 \mu\text{mol/L}$ after 1 year of treatment, females in the

control group had a mean iron level of $16.3 \mu\text{mol/L}$. All comparisons were statistically significant except when comparing the control group and the IBD group after 1 year of treatment.

No statistical differences in mean ferritin values were detected as males with IBD at the time of diagnosis had a mean ferritin level of $35 \mu\text{g/L}$ and $26 \mu\text{g/L}$ after 1 year of treatment; males in the control group had a mean ferritin level of $40 \mu\text{g/L}$. A similar trend was noted in the female subgroups. Female patients had a mean ferritin level of $30 \mu\text{g/L}$ and $18 \mu\text{g/L}$ after 1 year of treatment; females in the control group had a mean ferritin level of $31 \mu\text{g/L}$.

Differences in the prevalence of anemia between patients treated and not treated for anemia

The prevalence of anemia in patients with IBD treated for anemia was 89% at the time of diagnosis and 11% after 1 year (Table 2). Patients with IBD who were not treated for anemia had a prevalence of 46% and 17% at the time of diagnosis and after 1 year of treatment for the underlying disease, respectively. At the time of diagnosis, there was a statistically significant difference in hemoglobin concentration between patients who were treated for anemia and those who were not ($p = 0.009$). After 1 year of treatment, the hemoglobin concentration, MCV, and iron and ferritin levels between patients who were treated for anemia and patients who were not treated did not differ significantly.

When comparing patients with IBD who were treated for anemia at the time of diagnosis and after 1 year of treatment, the differences in hemoglobin concentration and iron level were shown to be statistically significant ($p < 0.0001$ for hemoglobin and $p = 0.004$ for iron). Additionally, there was a statistically significant difference in hemoglobin

Table 2. Blood parameters in patients with anemia who were and were not treated

	Treated for anemia	Prevalence of anemia	Mean hemoglobin (g/L)	Mean MCV (fl)	Mean iron ($\mu\text{mol/L}$)	Mean ferritin * ($\mu\text{g/L}$)
At the time of diagnosis	Yes	8/9 (89%)	103	75.7	5.1	38
	No	16/35 (46%)	120	77.8	7.4	32
P value			0.009	0.459	0.266	0.787
After 1 year of treatment	Yes	1/9 (11%)	136	82.9	16.3	22
	No	6/35 (17%)	133	82.6	11.2	23
P value			0.625	0.901	0.073	0.963
P ¹			< 0.0001	0.088	0.004	0.396
P ²			0.001	0.003	0.02	0.253

* only cases with CRP < 10 mg/L
P¹ – p value comparing values in patients treated for anemia at the time of diagnosis and after 1 year of treatment
P² – p value comparing values in patients not treated for anemia at the time of diagnosis and after 1 year of treatment

concentration ($p = 0.001$), MCV ($p = 0.003$), and iron level ($p = 0.02$) in patients with IBD who were not treated for anemia.

DISCUSSION

There was a high prevalence of anemia (63%) in all patients with IBD at the time of diagnosis; however, the prevalence of anemia decreased markedly after 1 year of treatment for IBD (18%). During that year, the patients with IBD were treated according to IBD guidelines. Additionally, 20% of the patients were treated for anemia with oral iron, intravenous iron, or diet supplements. The prevalence of anemia in patients with IBD in the current study was comparable to other studies which reported the prevalence of anemia in children with IBD to range from 41% to 73% (15, 29, 30). Goodhand et al. (10), using WHO criteria, reported a much higher prevalence of anemia in pediatric patients with IBD compared to adults (70%). A high prevalence of anemia in children with IBD at the time of diagnosis is an expected finding, as reported by other authors (10, 15, 29, 30). The fact that only a small percentage of patients with IBD were treated for anemia compared to standard treatment suggests that by treating IBD, the associated anemia is corrected and the hematologic parameters improve. Treating IBD may eliminate or mitigate some of the factors of the disease that can

influence erythrocyte balance, such as malabsorption of nutrients or inhibition of erythropoiesis due to inflammation, gastrointestinal bleeding, or dietary restrictions (17, 18); however, there should be an awareness of the potential to undertreat anemia.

Patients treated for anemia had decreased laboratory values at the time of diagnosis (mean hemoglobin = 103 g/l compared to 120 g/l in the group of patients who were not treated; $p = 0.009$), which is to be expected because the clinical status dictated specific treatment for anemia at the time. After 1 year, no significant difference existed between patients treated for anemia and patients who were not treated. The improvement in anemia was more frequent in patients treated for anemia (from 89% to 11%) than in patients who were not treated (from 46% to 17%), which could be due to effective anemia treatment and a higher percentage of anemia at baseline. The laboratory values of patients with IBD treated for anemia improved significantly between the time of diagnosis and after 1 year of treatment. Additionally, the laboratory values of patients with IBD who were not treated for anemia improved significantly after 1 year of treatment compared to the values at the time of diagnosis. These results indicate that both groups of patients (those who were treated for anemia and those who were not treated) received appropriate treatment because the laboratory values improved

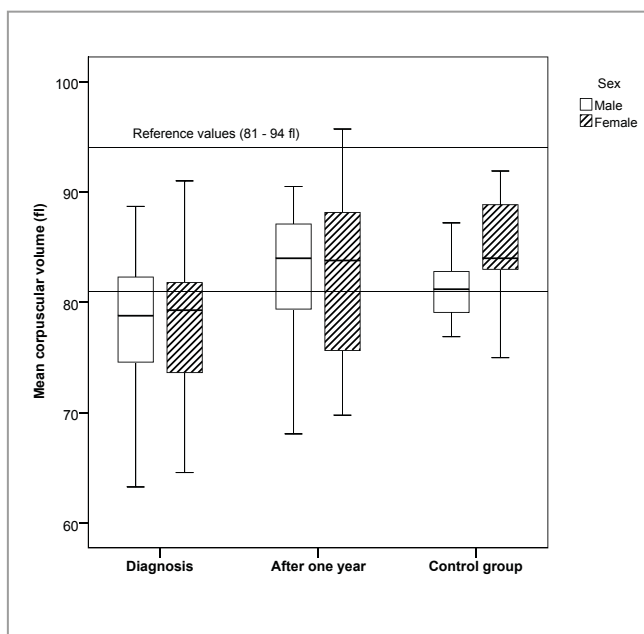


Figure 3. Mean corpuscular volume in different groups. Figure represents mean values of mean corpuscular volume (MCV) in all three groups (at the time of diagnosis and after 1 year of treatment, and the control group). Empty bars represent males and striped bars represent females. Values of MCV at the time of diagnosis are below reference values (81–94 fl). After 1 year of treatment, significant improvements in MCV are noted in males and females. Values of MCV after 1 year of treatment approach the values of the control group and are within the reference values.

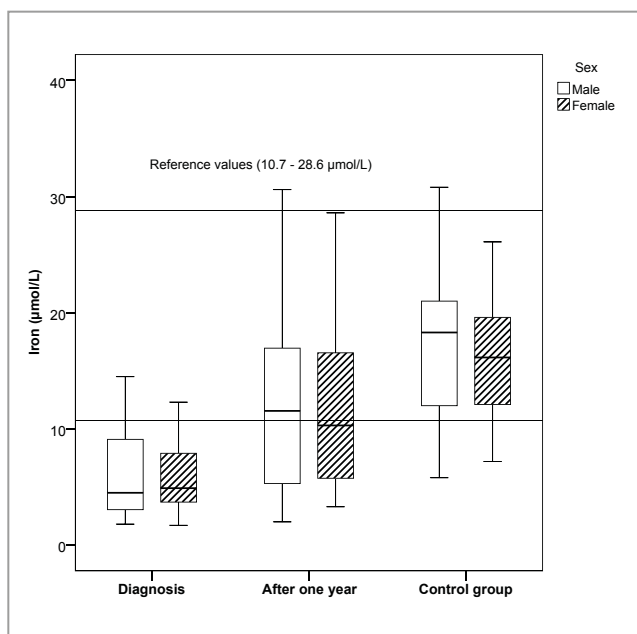


Figure 4. Iron in different groups. Figure represents serum iron levels in all three groups (at the time of diagnosis and after 1 year of treatment, and the control group). Empty bars represent males and striped bars represent females. Serum iron levels at the time of diagnosis are below reference values (10.7–28.6 µmol/L). After 1 year of treatment, significant improvements in iron are noted in males and females. Serum iron levels after 1 year of treatment approached the serum iron levels of the control group and are within the reference values.

significantly after 1 year of treatment. The fact that only 20% of the IBD patients were treated for anemia in the year following diagnosis is concerning.

We also observed improvements in blood parameters after 1 year of treatment, as shown by the results of blood parameters that approximated the levels in the control group. Specifically, the mean hemoglobin concentrations in male and female patients after 1 year of treatment increased to levels in the control group. The mean MCV and serum iron level increased above the minimum reference values (81.0 fl and 10.7 µmol/L, respectively).

Apparent underutilization of oral iron in pediatric care has several explanations. First, unlike adults (13, 23, 24), there is a lack of published evidence

to show that increasing the hemoglobin concentration in children with IBD by treatment with oral iron improves the QOL. Children tend to be more physically fit than adults, and although unproven, it is likely that children are more resilient to being anemic than adults, so there is no apparent clinical need to treat children (10). Second, pediatric gastroenterologists may be concerned about the possible side effects of supplemental iron. Oral iron is not always well tolerated in adults with IBD and is discontinued in approximately 10% of patients (12, 23) because of side effects, such as abdominal pain, diarrhea, and constipation (31). In contrast, no data exist regarding tolerance of oral iron in children with IBD. Another reason iron therapy is underused in children could be due to a concern about worsening disease, which was our top prior-

ity. For children with active IBD, the first priority is to achieve remission; thereafter, pediatric gastroenterologists may be reluctant to incur any risk, whether proven or not, of iron-induced relapse (10). Finally, there have been no studies involving oral iron efficacy in children with IBD, although oral iron is generally effective in children without IBD (32).

Children with IBD often experience low self-esteem and domestic conflicts caused by the stress of the disease, as well as an inability to take part in activities with their peers. Indeed, pediatric IBD patients with psychosocial support are better equipped to manage their disease (33). Adolescents with IBD have unique issues, such as poor medication adherence, growth failure, peer influence, and risky behavior, which make managing teenage IBD patients more challenging. It is important for physicians to recognize these issues so that they are prepared to intervene early with patients and parents (2).

The sample size of the IBD and control groups was a major drawback in this study. The small sample size reflects the relatively small number of IBD patients attending our clinic, which covers a relatively small geographic area. The retrospective nature of the study added to the lack of data, which further decreased our sample size.

CONCLUSION

Our results suggest that anemia improves when pediatric IBD patients are treated specifically for anemia, and also when treating the underlying disease only. We also found a small percentage of patients who were treated for anemia, which is an issue that must be addressed.

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REFERENCES

1. Matricon J, Barnich N, Ardid D. Immunopathogenesis of inflammatory bowel disease. *Self Nonself*. 2010; 1(4): 299–309.
2. Hyams JS. Chapter 333 – Inflammatory Bowel Disease. In: Kliegman RM, Behrman RE, Jenson HB, Stanon BF. *Nelson Textbook of Pediatrics*, 18th edition. Philadelphia: WB Saunders; 2007. p. 1575–85.
3. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*. 2007; 369(9573): 1641–57.
4. Gasche C. Anemia in IBD: the overlooked villain. *Inflamm Bowel Dis*. 2000; 6(2): 142–50.
5. Gisbert JP, Gomollón F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. *Am J Gastroenterol*. 2008; 103(5): 1299–307.
6. Gasche C, Berstad A, Befrits R, Beglinger C, Dignass A, Erichsen K, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2007; 13(12): 1545–53.
7. Gasche C, Lomer MC, Cavill I, Weiss G. Iron, anaemia, and inflammatory bowel diseases. *Gut*. 2004; 53(8): 1190–7.
8. Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. *Am J Med*. 2004; 116 Suppl 7A: 44S–49S.
9. Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. *Aliment Pharmacol Ther*. 2006; 24(11-12): 1507–23.
10. Goodhand JR, Kamperidis N, Rao A, Laskaratos F, McDermott A, Wahed M, et al. Prevalence and management of anemia in children, adoles-

- cents, and adults with inflammatory bowel disease. *Inflamm Bowel Dis.* 2012; 18(3): 513–9.
11. Abelson HT. Approach to the child with anemia. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ, editors. *Hematology: Basic Principles and Practice.* New York: Churchill Livingstone; 1991. p. 311–9.
 12. de Silva AD, Mylonaki M, Rampton DS. Oral iron therapy in inflammatory bowel disease: usage, tolerance, and efficacy. *Inflamm Bowel Dis.* 2003; 9(5): 316–20.
 13. Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. *Inflamm Bowel Dis.* 2006; 12(2): 123–30.
 14. Lakatos L, Pandur T, David G, Balogh Z, Kuronya P, Tollas A, et al. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. *World J Gastroenterol.* 2003; 9(10): 2300–7.
 15. Revel-Vilk S, Tamary H, Broide E, Zoldan M, Dinari G, Zahavi I, et al. Serum transferrin receptor in children and adolescents with inflammatory bowel disease. *Eur J Pediatr.* 2000; 159(8): 585–9.
 16. Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. *Nat Rev Gastroenterol Hepatol.* 2010; 7(11): 599–610.
 17. Lomer MC, Kodjabashia K, Hutchinson C, Greenfield SM, Thompson RP, Powell JJ. Intake of dietary iron is low in patients with Crohn's disease: a case-control study. *Br J Nutr.* 2004; 91(1): 141–8.
 18. Semrin G, Fishman DS, Bousvaros A, Zholudev A, Saunders AC, Correia CE, et al. Impaired intestinal iron absorption in Crohn's disease correlates with disease activity and markers of inflammation. *Inflamm Bowel Dis.* 2006; 12(12): 1101–6.
 19. Boyd HK, Lappin TR. Erythropoietin deficiency in the anaemia of chronic disorders. *Eur J Haematol.* 1991; 46(4): 198–201.
 20. Decaux G, Prosperit F, Horsmans Y, Desager JP. Relationship between red cell mean corpuscular volume and 6-thioguanine nucleotides in patients treated with azathioprine. *J Lab Clin Med.* 2000; 135(3): 256–62.
 21. Danese S, Semeraro S, Papa A, Roberto I, Scaldaferri F, Fedeli G, et al. Extraintestinal manifestations in inflammatory bowel disease. *World J Gastroenterol.* 2005; 11(46): 7227–36.
 22. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Morb Mortal Wkly Rep* 1998; 47(RR-3): 1–29.
 23. de Silva AD, Tsironi E, Feakins RM, Rampton DS. Efficacy and tolerability of oral iron therapy in inflammatory bowel disease: a prospective, comparative trial. *Aliment Pharmacol Ther.* 2005; 22(11-12): 1097–105.
 24. Gisbert JP, Bermejo F, Pajares R, Pérez-Calle JL, Rodríguez M, Algaba A, et al. Oral and intravenous iron treatment in inflammatory bowel disease: hematological response and quality of life improvement. *Inflamm Bowel Dis.* 2009; 15(10): 1485–91.
 25. Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr.* 2014 Jun; 58(6): 795–806.
 26. Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr.* 2012 Sep; 55(3): 340–61.
 27. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis.* 2014 Oct 1; 8(10): 1179–207.
 28. Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers. Geneva, World Health Organization, 2001 (WHO/NHD/01.3).

29. Beeken WL. Absorptive defects in young people with regional enteritis. *Pediatrics*. 1973; 52(1): 69–74.
30. Burbige EJ, Huang SH, Bayless TM. Clinical manifestations of Crohn's disease in children and adolescents. *Pediatrics*. 1975; 55(6): 866–71.
31. Rimon E, Kagansky N, Kagansky M, Mechnick L, Mashiah T, Namir M, et al. Are we giving too much iron? Low-dose iron therapy is effective in octogenarians. *Am J Med*. 2005; 118(10): 1142–7.
32. Zlotkin S, Arthur P, Antwi KY, Yeung G. Randomized, controlled trial of single versus 3-times-daily ferrous sulfate drops for treatment of anemia. *Pediatrics*. 2001; 108(3): 613–6.
33. Lu Y, Markowitz J. Inflammatory bowel disease in adolescents: what problems does it pose? *World J Gastroenterol*. 2011; 17(22): 2691–5.