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Iron Deficiency Is Common after Restorative Proctocolectomy with Ileal Pouch-Anal Anastomosis in Patients with Ulcerative Colitis

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Keywords
Ulcerative colitis · Iron deficiency · Ileal pouch-anal anastomosis · Restorative proctocolectomy

Abstract
Background: Micronutrient deficiencies may occur after restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA) in patients with ulcerative colitis (UC), largely due to malabsorption and/or pouch inflammation. ***Objectives:*** The objective of this study was to report the frequency of iron deficiency in patients with UC who underwent RPC with IPAA and identify associated risk factors. ***Methods:*** We conducted a retrospective chart review of patients with UC or IBD-unclassified who underwent RPC with IPAA at Mount Sinai Hospital between 2008 and 2017. Patients younger than 18 years of age at the time of colectomy were excluded. Descriptive statistics were used to analyze baseline characteristics. Medians with interquartile range (IQR) were reported for continuous variables, and proportions were reported for categorical variables. Iron deficiency was defined by ferritin <30 ng/mL. Logistic regression was used to analyze unadjusted relationships between hypothesized risk factors and the outcome of iron deficiency. ***Results:*** A total of 143 patients had iron studies a median of 3.0 (IQR 1.7–5.6) years after final surgical stage, of whom 73 (51.0%) were men. The median age was 33.5 (IQR 22.7–44.3) years. Iron deficiency was diagnosed in 80 (55.9%) patients with a median hemoglobin of 12.4 g/dL (IQR 10.9–13.3), ferritin of 14 ng/mL (IQR 9.0–23.3), and iron value of 44 μg/dL (IQR 26.0–68.8). Of these, 29 (36.3%) had a pouchoscopy performed within 3 months of iron deficiency diagnosis. Pouchitis and cuffitis were separately noted in 4 (13.8%) and 13 (44.8%) patients, respectively, and concomitant pouchitis-cuffitis was noted in 9 (31.0%) patients. Age, sex, anastomosis type, pouch duration, and history of pouchitis and/or cuffitis were not associated with iron deficiency. ***Conclusion:*** Iron deficiency is common after RPC with IPAA in patients with UC. Cuffitis is seen in the majority of patients with iron deficiency; however, iron deficiency may occur even in the absence of inflammation.

Introduction

Micronutrient deficiencies may occur after restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA) in patients with ulcerative colitis (UC) due to alteration of the gastrointestinal tract, fecal stasis, changes in mucosal morphology, and inflammation [1].

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Low levels of fat-soluble vitamins (A, D, E) have been reported in patients with IPAA presumed to be secondary to bacterial overgrowth, de-conjugation of bile salts, and disruption of chylomicrons responsible for absorption [2]. Low levels of B12 have similarly been noted in patients with IPAA, theorized to be a result of bacterial utilization in the setting of fecal stasis [3].

Iron deficiency has also been reported in patients with UC after IPAA with an incidence range of 30.0–62.5% [4, 5]. Pouchitis has been purported to be the most common cause of iron deficiency after IPAA, present in 50–100% of patients with low iron [4, 5]. However, while iron deficiency in the setting of pouchitis may be due to chronic blood loss from mucosal breaks, iron deficiency can still occur in the absence of pouchitis, albeit through unclear mechanisms. The majority of iron absorption occurs in the duodenum and proximal jejunum which are segments of the gastrointestinal tract that remain intact during the stages of RPC with IPAA and are not typically impacted by inflammation that could impair iron absorption. In the absence of pouchitis, potential etiologies for iron deficiency after IPAA include anastomotic ulcers, insufficient oral intake, or cuffitis [4, 6].

Few studies to date have studied risk factors for iron deficiency after IPAA. No significant age or sex differences have been seen in the prevalence of iron deficiency after IPAA, and no associations between pouch configuration and iron deficiency have been noted [4–7]. In addition, no studies have shown a relationship between pre-colectomy and post-IPAA iron deficiency; in fact, Nicholls et al. [8] saw improvement in iron levels post-IPAA, likely a result of UC treatment via colectomy. In light of limited data, the aim of this study was to report the frequency and associated risk factors of iron deficiency in patients with UC who underwent RPC with IPAA at a high-volume, single-center tertiary care hospital.

Materials and Methods

This was a retrospective cohort analysis of patients with UC or IBD-unclassified who underwent RPC with IPAA at Mount Sinai Hospital for medically refractory disease or dysplasia between January 2008 and December 2017. This retrospective research was approved by the Mount Sinai IRB, study-16-01321. The data for this study were obtained from a retrospective medical-surgical database that included only patients over the age of 18 who underwent RPC with IPAA at Mount Sinai Hospital. Collected patient demographics and clinical characteristics included age, sex, number of surgical stages, type of anastomosis (handsewn vs. stapled), rectal cuff length, iron and hemoglobin assessments, and results of endoscopy and pouchoscopy. Only iron and hemoglobin assessments performed greater than 12 months after the final surgical stage were included. This minimum 12-month interval was used to prevent conflation of iron deficiency or anemia that may be residual from active colitis or related to surgical complications.

Descriptive statistics were used to analyze the baseline characteristics and laboratories of the study population. Medians with interquartile range (IQR) were reported for continuous variables, and proportions were reported for categorical variables. Iron deficiency was defined as a ferritin <30 ng/mL [9]. Anemia was defined as a hemoglobin <13.0 g/dL in men and <12.0 g/dL in women [10]. Logistic regression was used to analyze unadjusted relationships between hypothesized risk factors and outcomes. Odds ratios and 95% confidence intervals are reported. All analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA). Two-sided p values <0.05 were considered statistically significant.

Table 1. Patient demographics and clinical characteristics in patients with iron assessments (n = 143)

Demographics and disease characteristics	
Age (median), years	33.53
Sex, *n* (%)	
Men	73 (51.1)
Women	70 (48.9)
Body mass index (mean)	21.87
Pouch duration, years (mean)	46.05
Median rectal cuff length, cm	1.5
Anastomosis type, *n* (%)	
Stapled anastomosis	100 (69.9)
Handsewn anastomosis	43 (30.1)
Prior pouch complications, *n* (%)	
History of pouchitis	78 (54.5)
History of cuffitis	39 (27.2)

Results

A total of 664 patients underwent RPC with IPAA between January 2008 and December 2017. Serum iron assessment was performed in 143 patients a median of 3.0 (IQR 1.7–5.6) years after the final surgical stage. Of these, 73 (51.0%) were men, and the median age was 33.5 (IQR 22.7–44.3) years. The pouch-anal anastomosis was stapled in 100 (69.9%) patients and handsewn in 43 (30.1%). The median rectal cuff length was 1.5 cm [1, 2]. Complete patient demographics and clinical characteristics are noted in Table 1.

The following median values were noted in the 143 patients: hemoglobin 13.2 g/dL (IQR 12.0–14.3), mean corpuscular value 86 fL (IQR 81.6–90.5), iron 59.5 μg/dL (IQR 34.0–84.0), ferritin 39 ng/mL (IQR 17.0–79.5). Iron deficiency was diagnosed in 80 (55.9%) patients with a median hemoglobin of 12.4 g/dL (IQR 10.9–13.3), ferritin of 14 ng/mL (IQR 9.0–23.3), and iron value of 44 μg/dL

(IQR 26.0–68.8). Using a hemoglobin <13.0 g/dL in men and <12.0 g/dL in women, 84% of men and 46% of women with iron deficiency were anemic. Of the patients found to be iron deficient, 20 (25%) were treated with iron supplementation within 6 months of being found to be iron deficient – 6 (30.0%) with intravenous iron infusions and 10 (50%) with oral iron. Four (20%) patients received both intravenous and oral iron during their treatment course. Repeat iron assessments were performed in 10 (50%) of the patients who were prescribed iron supplementation, of whom 7 (70%) were still found to be iron deficient.

Endoscopy was performed in 11 (13.8%) patients for evaluation of iron deficiency within 6 months of diagnosis. Of these, 5 (45.5%) had a normal exam with no etiology for iron deficiency noted; however, 5 (45.5%) had gastric erosions/ulcers, 3 (27.3%) gastric erythema, 2 (18.2%) duodenal erosions/ulcers, and 1 (9.0%) duodenal erythema. Biopsies were performed in 10 (90.1%) patients and were negative for Helicobacter pylori in all. Pouchoscopy was performed in 29 (36.3%) patients for evaluation of iron deficiency within 3 months of diagnosis. Pouchitis and cuffitis were separately noted in 4 (13.8%) and 13 (44.8%) patients, respectively, and concomitant pouchitis-cuffitis was noted in 9 (31.0%) patients. On univariate logistic regression analysis, age, sex, type of anastomosis, pouch duration, and history of pouchitis and/or cuffitis were not predictive of iron deficiency.

Discussion

In this large single-center retrospective study evaluating iron deficiency after RPC with IPAA, approximately 20% of patients had iron levels assessed, and 55.9% were found to be iron deficient, of whom only 25% received iron supplementation. The majority of patients with iron deficiency who underwent endoscopy and/or pouchoscopy were noted to have cuffitis, suggesting the etiology was chronic blood loss from cuff mucosal breaks or erosions; however, no clinical factors were significantly associated with iron deficiency. Interestingly, there was a subset of patients in this study with iron deficiency however normal hemoglobin. Iron deficiency in the absence of anemia has been shown to cause weakness, fatigue, neurocognitive dysfunction and may be the first sign of impending anemia [11, 12].

Iron deficiency is common after RPC with IPAA, typically related to underlying pouchitis and resultant chronic blood loss. Pastrana et al. [5] reviewed a cohort of 18 patients with UC who underwent IPAA and found that approximately 55.5% had iron deficiency, 100% of whom had pouchitis. Similarly, Jaboli et al. [4] conducted a study with 74 patients who underwent IPAA and were found to have iron deficiency, 50% of whom had pouchitis. Iron deficiency after RPC with IPAA may also be related to cuffitis, an inflammatory condition of the residual rectum that occurs in up to 20% of patients [13]. In this study, the majority of patients with iron deficiency had cuffitis as the primary cause, likely related to a similar mechanism of ulcer-mediated chronic blood loss that occurs in pouchitis.

However, iron deficiency after IPAA may also occur in the absence of inflammation. In fact, in this study, 41.4% of patients with iron deficiency had no evidence of pouchitis or cuffitis. While only a small number of patients ultimately underwent endoscopy within 6 months of the iron deficiency diagnosis, the majority did have gastric erosions/ulcers that may have contributed to blood loss. In Jaboli et al. 's [4] study, 11 of 24 (45.8%) patients with iron deficiency after IPAA also had a video capsule endoscopy to assess the underlying cause, of whom 4 had small bowel erosions and 1 had angiodysplasia. These finding suggest endoscopy and small bowel evaluation with a video capsule should be considered in patients with iron deficiency after IPAA, particularly if the pouchoscopy is normal.

Only a minority of patients in this study had iron levels checked after RPC with IPAA despite consensus guidelines recommending routine assessment every 6–12 months [10]. Furthermore, only 25% of patients were prescribed iron supplementation despite guidelines that recommend iron supplementation in all patients with iron deficiency with or without anemia, and only 30% of patients received intravenous iron as first-line therapy despite consensus guidelines that note the superiority of intravenous iron over oral [10, 14]. Finally, only 50% of patients had repeat iron assessments after supplementation. Taken together, these results highlight the lack of regular surveillance that may occur after IPAA and the significant need for routine iron assessment and supplementation if indicated.

The major limitations of this study include its retrospective nature and risk of selection bias. Most patients in this study did not undergo routine post-IPAA iron assessment or endoscopy and pouchoscopy; therefore, the true incidence of iron deficiency and its causes may be underreported. In addition, the majority of patients with iron deficiency did not have corresponding pre- and post-IPAA iron assessments, limiting the ability to delineate whether the iron deficiency was residual from the preoperative period or new from the postoperative period. Finally, we used the

strictest definition possible for iron deficiency with a ferritin <30 μg/L; however, ECCO guidelines stipulate that in the presence of inflammation, a ferritin up to 100 μg/L can be diagnostic for iron deficiency as ferritin is an acute phase reactant [10].

In conclusion, this study highlights the high frequency of iron deficiency in patients with UC who have undergone RPC with IPAA. Iron deficiency may occur in the presence or absence of pouchitis or cuffitis and may not necessarily be associated with anemia. We propose routine iron assessment every 6–12 months with intravenous iron supplementation if indicated in patients with UC who have undergone RPC with IPAA. A thorough evaluation with endoscopy and/or capsule endoscopy should be considered in patients with iron deficiency and a normal pouchoscopy to potentially identify etiologies other than pouchitis and cuffitis.

Statement of Ethics

This retrospective research was approved by the Mount Sinai IRB, study-16-01321. Written informed consent from participants was not required in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors had significant contributions to this study. I.D. contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript. T.A. and M.P. contributed to acquisition of data and critical revision of the manuscript. S.K., P.S., A.G., and M.C.D. contributed to critical revision of the manuscript. M.K. contributed to study concept and design, acquisition of data, statistical analysis, interpretation of data, drafting of the manuscript, and critical revision of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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