Chapter 4
Diagnosis and Management of Iron Deficiency in Inflammatory Bowel Disease

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Introduction

Iron is a critical element and essential for fundamental metabolic processes in cells with a major role in oxygen (O_2) carry (hemoglobin), muscle function (myoglobin), and mitochondrial processes [1]. Despite this fundamental role in human metabolism, there is a narrow balance between iron supply and absorption on one side, and iron demand on the other. Iron deficiency is the most common nutritional deficiency [2] and the leading cause of anemia worldwide [3–5]. In the United States, prevalence of iron deficiency ranges from 4.5 to 18.0 % [6–8], while 50 % of anemia worldwide is thought to be caused by iron deficiency [9]. A number which seems huge given 2.2 billion people globally affected by anemia [4].

While iron deficiency is a common medical condition, clinical presentation is rather nonspecific with most of cases remaining undiagnosed therefore. Among the most frequently reported symptoms are paleness, fatigue, headache, and dyspnea [2, 10–12]. In contrast, more typical findings such as tachycardia, vertigo, or even syncope are less often reported and suggest severe states of anemia [13, 14]. Due to its mostly chronic and asymptomatic disease course, a majority of cases are identified

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based on routine laboratory work-up including hemoglobin and ferritin. Thus, regular laboratory testing including screening for iron deficiency and anemia is indicated particularly in those patients with a high risk of decreased iron supply such as vegetarians or children, those with impaired intestinal absorption (celiac disease or inflammatory bowel disease), increased blood (intestinal tumors or intestinal parasites), or the presence of chronic inflammation with a combination of anemia of chronic disease and iron deficiency anemia. However, most of the cases with iron deficiency anemia are seen in otherwise healthy patients showing an increased iron demand such as pregnant women, adolescents, or athletes [2]. Awareness of a mostly chronic and asymptomatic disease course is especially important regarding the possible consequences of iron deficiency, among which are impaired quality of life and the ability to work, increased hospitalizations and health care costs [15–17].

In inflammatory bowel disease patients, anemia is the most common systemic complication and extraintestinal manifestation [18–21]. Prevalence ranges from 9 to 74 % [22]. Iron deficiency anemia accounts for the majority of anemic patients followed by anemia of chronic disease [23, 24]. While the former develops as the consequence of iron deficiency (decreased intake or intestinal absorption, continuous or recurrent blood loss), the latter is caused by inflammatory processes. However, the two types are frequently overlapping [23]. Other causes are vitamin B12 deficiency, folic acid deficiency or toxic effects of medications. Given the above-mentioned consequences of untreated iron deficiency and anemia, these two IBD complications are more than just laboratory markers [20]. Prevention and treatment of those conditions is key in the management of IBD patients and awareness of those is especially important given the frequent recurrence despite adequate and successful anti-inflammatory therapy [25].

In this chapter, we focus mainly on iron deficiency anemia and discuss the most important physiological mechanisms in human iron cycle, diagnostic steps in clinical practice, and therapeutic approaches in IBD patients with iron deficiency. Recommendations regarding screening, treatment, and prevention of iron deficiency and anemia are mainly based on the current European Crohn's and Colitis Organisation (ECCO) Guidelines [25].

The Iron Cycle

The only physiological way of iron uptake is via intestinal absorption, which additionally represents the critically controlled process in iron metabolism [1]. In contrast, excretion of iron is not regulated and loss of iron happens in a non-controlled way via desquamation of skin, intestinal epithelial cells, or blood loss (e.g., menstruation). Normally, 1–2 mg iron is lost through these mechanisms [26]. While human body contains 3–5 g total iron, 20–25 mg is needed for production of red blood cells and cellular metabolism daily [26]. Most of the needed iron can be recycled from senescent blood cells by the reticuloendothelial system (RES) [1]. However, uncontrolled loss of iron has to be compensated by intestinal absorption only.

Thus, margins between intestinal uptake und iron requirements are narrow. Dietary iron is available in two forms as heme and non-heme iron; the former consists of Fe^{2+} (ferrous iron) and can be found in animal food sources such as meat or poultry, the latter consists of the ferric ion (Fe^{3+}), which is present in vegetarian foods [2, 27]. Iron is transported through the intestinal brush border via a divalent metal transporter (DMT1) only in its ferrous form; [28] Iron from vegetarian food has to be reduced by a membrane-associated ferrireductase DcytB first [29]. Thus, absorption rates of iron from animal sources are generally higher [2]. At the basolateral membrane, Ferroportin transports iron into systemic circulation [30, 31] where it is transformed to its ferrous form again by a multicopper oxidase homologous to ceruloplasmin [1]. In its ferrous form, iron is finally able to bind to Transferrin, an iron-transporting protein. The iron-Transferrin complex consequently binds cells expressing a Tf-binding protein on its surface, among which erythroblasts in the bone marrow are the most important and most frequent [1].

Iron absorption needs a close control in order to up- or down-regulate intestinal uptake in accordance with body requirements. This narrow homeostasis is basically controlled by hepcidin, a peptide hormone synthesized in the liver, which allows immediate adjustments of iron fluctuation by binding to and inducing degradation of ferroportin [32]. Hepcidin itself is increased in the presence of iron overload, systemic inflammation, and/or infection [1, 33], which partly explains the overlap of anemia of chronic disease in inflammatory disorders and iron deficiency. In contrast, Hepcidin decreases in the presence of iron deficiency, tissue hypoxia, or increased erythropoiesis [1, 3].

Iron Deficiency and Anemia in IBD Patients

Extraintestinal manifestations (EIM) of IBD are frequently observed with a prevalence ranging from 6 to 47 % [34–41]. They considerably affect morbidity and mortality in IBD patients [42, 43]. Besides typical EIM such as arthritis, uveitis, or skin changes, which are seen as reactive to underlying IBD, systemic manifestations may also include IBD-related complications due to metabolic abnormalities such as nephrolithiasis, amyloidosis, osteopathy, or anemia [41]. Nonetheless, compared to classical EIM, anemia in IBD has received only little attention [23], as it may be too common to be specifically recognized as a complication [44]. In addition, treating anemia has often low priority [44]. However, prevalence of anemia in IBD seems to be high, although studies show differences ranging from 9 to 74 % [22]. A recent review showed a mean prevalence of 17 %, increasing up to 68 % in those patients hospitalized for IBD [21]. Thus, anemia can be considered as one of the most common systemic complications of acute IBD [23]. Iron deficiency, which is the most frequent cause of anemia in IBD, is seen in 36–90 % of all IBD patients [19]. Although chronic blood loss and decreased iron absorption leads to iron deficiency with a consecutively developing anemia, anemia in IBD patients is often multifactorial with the two main causes of iron deficiency [45] and anemia of

chronic disease [46]. Further possible causes are drug toxicity (sulfasalazine, thiopurines), IBD-associated autoimmune hemolysis, myelodysplastic syndrome, or impaired absorption of vitamin B12 or folate [23].

Independent of the underlying mechanism, anemia has been recognized as a key symptom in IBD [44]. Furthermore, the impact of anemia on quality of life of IBD patients is substantial [25]. Several studies have shown impaired quality of life for anemia in general patients [47, 48] and in those affected with IBD [17, 18, 22, 44]. Even in the absence of specific symptoms, anemia seems to impair quality of life [15, 17, 23]. Of note, quality of life may be as low as in anemic patients with advanced cancer and anemia in IBD patients seems to raise comparable concerns as abdominal pain or diarrhea does [44, 49]. In addition to an impaired quality of life, anemia negatively affects the ability to work, hospitalization, and health care costs [16, 25]. Thus, anemia is more than just a common feature of IBD; it is of great clinical relevance for the patient [23]. Doctors caring for IBD patients should be more aware of this frequent medical condition.

Diagnosis of Iron Deficiency and Anemia

Anemia in IBD is defined indifferent to other conditions. The cut-off limits according to the WHO definition can be applied in all IBD patients [25]. However, inter-individual differences and modulating factors such as age, gender, pregnancy, high altitude, smoking, and ethnicity should be taken into account [50, 51]. According to the World Health Organization WHO, minimum hemoglobin levels used to define anemia in white people living at sea level are: 12.0 g/L for non-pregnant women, 13.0 g/L for men. Iron deficiency is usually diagnosed by serum ferritin. Lower limits are defined according to the level of systemic inflammation. In the absence of biochemical (assessed by CRP, ESR, and leukocyte count) and clinical evidence (assessed by CDAI, CDEIS, Mayo Score) of inflammation, serum ferritin cut-off level for the presence of iron deficiency is <30 μg/L [25]. Definition of iron deficiency in the presence of systemic inflammation is rather challenging. A serum ferritin up to 100 μg/L may still be consistent with iron deficiency. In such cases, concentration of soluble transferrin receptor (sTfR) in the serum and sTfR/log ferritin index have been shown to be an indicator of iron supply available for erythropoiesis and therefore to help distinguish between iron deficiency anemia and anemia of chronic disease [52–55]. A serum ferritin of more than 100 μg/L likely excludes true iron deficiency [44, 56]. In addition an sTfR/log serum ferritin ratio of less than 1 is useful to exclude true iron deficiency in anemia of chronic disease [52, 56]. However, anemia of chronic disease often goes along with functional iron deficiency, which is indicated by a transferrin saturation (TfS) <20 % [25].

Screening for anemia and iron deficiency is recommended in all IBD patients and consists of complete blood count, serum ferritin, and CRP. Screening should be repeated every 6–12 months for all patients in clinical remission, while anemia and iron deficiency screening should be at least performed every 3 months in those IBD

patients with active disease [25]. In addition, vitamin B12 and folic acid should be measured regularly, at least every year, but more often in high-risk patients with ileal resection or those showing macrocytosis. Anemia work-up is indicated in all patients showing hemoglobin below normal limits and should include the following parameters: red blood cell indices (RDW, MCV), reticulocyte count, differential blood count, transferrin saturation, CRP, and serum ferritin. Based on a hematologic algorithm, most of the anemia forms can be easily classified without additional measurements. More extensive work-up includes serum concentrations of vitamin B12, folic acid, haptoglobin, the percentage of hypochromic red cells, reticulocyte hemoglobin, lactate dehydrogenase, soluble transferrin receptor, creatinine, and urea [25]. If the cause of anemia remains unclear after extensive work-up, referral to a hematologist is recommended.

Treatment of Iron Deficiency and Anemia in IBD Patients

Every IBD patients with iron deficiency anemia should be treated given significant improvements regarding quality of life [17, 57]. Intravenous iron supplementation is favored over oral supplementation in IBD patients for different reasons. The intravenous formulas are more effective, lead to a faster response, and are generally better tolerated [58–61]. They have been shown to be safe, effective, and well tolerated for the correction of iron deficiency anemia in IBD patients in several trials [57, 60, 62, 63]. In the presence of intestinal inflammation, iron absorption is limited and non-absorbed iron can be exposed to the ulcerated intestinal surface, which may lead to mucosal harm and even disease exacerbation [64–67]. Thus, oral supplementation is actually only recommended for those patients with mild anemia, absence of intestinal inflammatory activity, and no prior intolerance to oral regimens [25]. No more than 100 mg elemental iron per day is recommended; higher doses may lead to more side effects and therefore lower compliance. However, in most cases low dose oral iron is effective [68–70]. Oral iron-containing preparations differ regarding dosage, salt, chemical state of iron (ferrous or ferric), and galenic form (quick vs. prolonged release.) [71] In non-IBD iron deficiency anemia, bivalent iron preparations are of high efficacy, acceptable tolerability (especially as prolonged-release formulation), and low cost, while trivalent preparations have a poorer absorption and are more expensive [71]. The four commonly available ferrous iron supplementations are: ferrous sulfate, which is the standard treatment, ferrous sulfate exsiccated, ferrous gluconate, and ferrous fumarate [2]. In contrast to non-IBD conditions, where oral supplementation is considered first-line in most cases, intravenous iron should be considered as first-line treatment in the majority of IBD patients with iron deficiency anemia. The primary goal in IBD patients with iron deficiency anemia is normalization of hemoglobin levels and iron stores. Importantly, serum ferritin levels should not be measured within the first 8 weeks after intravenous supplementation given possible interference and false-high values [72]. Six different intravenous regimens are available for treatment of iron

deficiency anemia: iron sucrose, ferric gluconate, ferric carboxymaltose, iron isomaltoside-1000, ferumoxytol, and iron dextran (low-molecular-weight forms) [2]. High-molecular-weight iron dextran has been withdrawn from the market due to higher frequency of serious adverse events including anaphylactic reactions [73], while low-molecular-weight forms show a safety profile comparable to other intravenous iron formulations [74]. Practical guidelines recommend slow infusion rates, patient observation, and administration in an adequate setting with access to resuscitation facilities to further minimize risk of serious adverse events [3, 73, 74]. Different compositions of these formula lead to different iron release rates, which determine the amount of iron given as a single dose. Table 4.1 summarizes the currently available intravenous iron formulations according to reviews by Larson [75] and Auerbach [76]. The dose needed for intravenous supplementation can be calculated with the Ganzoni's formula: body weight in kg × 2.3 × hemoglobin deficiency (target hemoglobin level—patient hemoglobin level) + 500–1000 mg iron [77]. However, a simplified scheme has been established and seems to be of better efficacy and compliance than the Ganzoni's formula [57]. The estimation of total iron need can be based on baseline hemoglobin and body weight only. Although this scheme has only been tested for ferric carboxymaltose in the FERGIcor trial [57], it can also be applied for dosing of other intravenous iron formulations.

In contrast to iron deficiency anemia, treatment recommendations for IBD patients with iron deficiency, but without anemia are rather controversial [25]. There is some evidence for a benefit of treating iron deficiency before development of anemia with studies showing improvement of fatigue or physical performance in women of reproductive age and in other conditions such as heart failure [78–80].

Table 4.1 Intravenous iron preparations (according to Larson [75] and Auerbach [76])

	Molecular weight (kDa)	Test dose	Preservatives	Maximal single dose	Higher doses (off label use)
LMW Dextran (CosmoFer®, INFeD®)	165	Yes (25 mg 15–30 min)	None	100 mg (>30 s)	Total dose infusion over 4 h
Iron sucrose (Venofer®)	34–60	No	None	200 mg (2–5 min)	300 mg over 1 h
Ferric gluconate (Ferrelcit®, Nulecit®)	289–444	No	Benzyl alcohol	125 mg (10 min)	250 mg (15 min)
Ferumoxytol (Feraheme®)	750	No	None	510 mg (<1 min)	no
Ferric carboxymaltose (Injectafer®, Ferinject®)	150	No	Intravenous iron preparationsNone	750 mg (slow push or over 15 min)	no
Iron isomaltoside (Monofer®)	150	No	None	20 mg/kg (30–60 min)	no

However, data about treating iron deficiency in IBD patients is lacking hitherto. Current guidelines recommend iron supplementation depending on patients' history, symptoms, and individual preferences [25].

How to Prevent Iron Deficiency and Anemia in IBD Patients

Given a strong correlation between intestinal disease extent and activity on one side and blood loss and severity of anemia on the other, treatment of underlying disease activity is key in both treatment and prevention of iron deficiency and anemia [19, 81, 82]. Recurrence of anemia is often an indicator for persistence of intestinal disease activity and warrants further investigation of possible subclinical disease activity [25]. After successful treatment of iron deficiency anemia, patients should be followed up closely given a high rate of recurrence in the first year thereafter [62, 83]. Guidelines recommend monitoring with full blood count and ferritin levels every 3 months for the first year and every 6–12 months thereafter [25]. Interestingly, a study could show a relation between the size of post-treatment iron stores and the speed of recurrence of iron deficiency anemia in IBD patients [83]. A cut-off level of more than 400 μg/L prevented recurrence significantly better than levels below [83]. Of note, the FERGImain trial showed significantly lower recurrence rates in those patients, where iron supplementation was reinitiated if ferritin levels fell below 100 μg/L, which was assessed at 2-months intervals [62]. In addition, those patients receiving preventive iron supplementation reported less gastrointestinal symptoms and IBD flares than those without [62]. Thus, a proactive approach is recommended rather than just a watch-and-wait strategy and such an approach seems to be cost-effective given the possible savings compared to anemic IBD patients [84].

Other anemia treatment options such as erythropoiesis-stimulating agents or even blood transfusion should be considered only in those patients with anemia of chronic disease who have shown insufficient response to intravenous iron supplementation and who continue to have low hemoglobin levels despite adequate anti-inflammatory treatment including biologic agents. Blood transfusion should be restricted to those patients with a hemoglobin concentration of less than 7 g/dL or above if anemia is symptomatic or if comorbidities such as coronary artery disease are present [85–87]. In most patients, even hemoglobin levels of less than 7 g/dL can be tolerated in the meantime. Iron supplementation remains key in those patients receiving erythropoiesis-stimulating factors or blood transfusions.

What to Tell Patients?

Screening for iron deficiency and anemia is key in management of IBD patients and should not depend on clinical symptoms given a mostly chronic and asymptomatic disease course. Dietary iron from animal food sources are better absorbed than iron

present in the vegetarian diet [88]. Anemia should be seen as a systemic manifestation of IBD comparable to other EIM such as arthritis or skin problems [20]. Possible impact of anemia on quality of life and the ability to work should be discussed with IBD patients and treatment for anemia should be started in every patient fulfilling WHO criteria of iron deficiency anemia [16, 25]. Intravenous iron supplementation should be first-line therapy and oral supplementation only seems to be an option in those patients with mild anemia, absence of intestinal disease activity, and no history of prior intolerance. Oral iron supplementation may even exacerbate disease activity in IBD patients with intestinal inflammation [64–67]. Controversy about evidence of iron supplementation in patients with iron deficiency without anemia should be discussed with the patient in detail and decision about supplementation or not should be based on clinical presentation, patient's history, and individual preferences. Information about frequent and fast recurrence of anemia despite adequate treatment should be provided with a close follow-up during the first year [62, 83]. Patients with a drop-down in their serum ferritin below 100 μg/L should be motivated to reinstall intravenous iron supplementation [62]. Data about possible prevention of disease flares by this proactive approach should be provided. Last but not least, proactive prevention of recurrence of iron deficiency should be seen as cost-effective given the possibility of preventing anemic IBD patients and their consequences [84].

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