Review Article

Iron deficiency in chronic inflammatory bowel diseases: an update

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Abstract: Iron deficiency (ID) is the most frequent nutritional deficiency worldwide, with more than 1.2 billion affected individuals with anemia and probably more than double without anemia. ID can be either absolute by a relative insufficiency of intakes, loss excess, or functional, mainly due to inflammation. Inflammatory bowel diseases (IBD) include Crohn's disease, ulcerative colitis, and unclassified inflammatory bowel disease, which share a common trait chronic inflammation of the digestive tract wall. These diseases are increasing worldwide over the years. The ID is relatively frequent in IBD (up to 76% of patients in some studies, ID is underdiagnosed and under-treated in this setting, generally when the deficiency is not associated with anemia, which is the cardinal symptom of this extra digestive complication. Indeed, the current use of ferritin assay, which is abnormally high in those diseases, due to inflammation, is probably the main reason for this underdiagnosis. The adjunction of the calculation of transferrin saturation and the exploration of other nutritional deficiencies are recommended in the diagnosis and in the follow-up of the diseases, notably to help treat the intense asthenia that patients often report. Herein, we aimed to present an overview of ID prevalence, physiopathology, diagnosis, and treatment considerations in IBD patients.

Keywords: Iron; Chron's disease; ulcerative colitis; anemia; ferritin; transferrin saturation

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Introduction

Iron deficiency (ID) is the most widespread nutritional deficiency in the world. The ID appears first without anemia, and later, microcytic hypochromic anemia can occur. Iron deficiency could affect more than 1.2 billion affected individuals with anemia and probably more than double without anemia (1).

Inflammatory bowel diseases (IBD) are common gastrointestinal diseases that include Crohn's disease (CD), ulcerative colitis (UC), and inflammatory bowel disease unclassified (IBDU). Those chronic diseases share as a common trait inflammation of the wall of part of the gastrointestinal tract, associated with abdominal pain, frequent and possibly bloody diarrhea, sometimes anal lesions, and other extra-digestive manifestations (notably articular, cutaneous, ocular, hepatic). The diagnosis of IBD is currently multidisciplinary, based on clinical, biological, and medical imaging criteria. The incidence of IBD has been shown to increase worldwide over time. IBD thus represent significant health and economic burden for developed countries (2). More than 2.5 million European individuals and 1.5 million in the USA suffer from these diseases (3). These diseases are frequently identified in young people ranging from 20 to 30 years (4). However, those diseases can occur at any age, notably earlier, since 15% of patients are children (5).

IBD are characterized by inflammatory episodes, varying in intensity and duration, and alternating with remissions. The inflammatory disease can affect the whole

digestive tract in CD, from the mouth to the rectum. Most frequently, CD affects only the small intestine and the beginning of the large intestine. These lesions occur by patches and leave healthy mucosa pieces between inflammatory areas. Conversely, in UC, injuries are continuous and generally range between the colon to the rectum. The origins of IBD are complex, and the etiology of IBD is only partly understood. The family aggregation has long been identified (2), with a polygenic heritability suggested. A genetic predisposition and a dysregulation of the immune system have been identified in the pathophysiological process. Moreover, some environmental factors, including the microbiome, could also participate in the genesis of the disease.

Iron deficiency

Iron is the essential component of hemoglobin, mainly found in the erythrocytes, and myoglobin in muscles, which contain around 80% of total body iron. The iron is also mandatory for cellular respiration, energy production, DNA synthesis, and cell proliferation (6,7), mainly as a prosthetic group in hemoproteins. Iron deficiency is due to an insufficient supply of iron to meet the requirements of the body. The daily loss is estimated to be within 1–2 mg/day. In its most evolved form, iron deficiency is associated with microcytic anemia (8). Iron deficiency with or without anemia can is related to other non-hematologic symptoms. Iron deficiency may be related to fatigue, a negative impact on life's quality, a productivity decrease (9,10), and delayed growth and development in children (11). Iron deficiency is a significant public health problem because undiagnosed and untreated and causes more than 60% of anemia worldwide. All-cause anemia is associated with increased morbidity and mortality in patients affected by inflammatory gastrointestinal diseases, cancer or kidney failure, and during and after surgery (12,13).

Absolute and functional ID are the two main clinic-biological profiles associated with the defect. Both are currently observed in IBD. A decrease in the total iron supply in the organism characterized absolute iron deficiency. It is related either to an insufficient iron intake or chronic blood loss, or, eventually, both. Functional iron deficiency is due to a defect in iron transport from the storage areas. A persistent inflammatory state with increased cytokines, particularly interleukin 6, together with the inappropriate increase of hepcidin, is the primary etiology of this functional deficiency (14). Hepcidin is a polypeptide synthesized primarily in the liver. This peptide is an acute-phase reactant that regulates the plasma iron concentration at the systemic level.

Hepcidin induces degradation by the internalization of ferroportin transporter. Ferroportin is also known as solute carrier family 40 member 1 (SLC40A1) or iron-regulated transporter 1 (IREG1). This transporter is a transmembrane protein. It is the only known iron exporter that permits iron transfer from intracellular to extracellular medium (15).

Absolute ID in patients with IBD could be due to increased loss and decreased intakes of iron: continuous or recurrent blood loss from the bowel and reduced iron intake, and limited iron absorption from the digestive system. Moreover, chronic inflammation should be associated with increased hepcidin, leading to a functional iron deficiency associated with absolute iron deficiency.

Iron deficiency in IBD

ID is probably underdiagnosed and undertreated in IBD in current clinical practice (16). The most frequent etiology of iron deficiency in patients with IBD should be an increased iron loss due to gastrointestinal blood loss. However, this absolute iron deficiency can also be related to decreased absorption and the pro-inflammatory climate associate with an increased interleukin six concentration.

In a multicentric Scandinavian study, 35% of IBD patients were iron deficient (17), 45% in patients with UC (18). This percentage rises as high as 76% in other cohorts (19), making iron deficiency the most common systemic complication of IBD.

However, iron deficiency is generally not systematically screened for in IBD patients. Fatigue, although not specific to iron deficiency, is a prevalent and disabling symptom in patients with IBD, and it is well-known that it is associated with iron deficiency. Nearly 80% of those patients with active disease and 50% with inactive IBD report substantial fatigue.

In a recent Spanish study, the prevalence of ID in IBD patients was as high as 37% (OR =2.9; P=0.015) (20). Iron deficiency was mostly observed in females. The presence of inflammatory activity (OR =9.4; P=0.001) was the main determinant factor associated with an iron deficiency, suggesting that the functional deficiency was more important than absolute iron deficiency, as previously evoked (21).

Anemia in IBD

Anemia is prevalent in patients with IBD: 14–19% of all

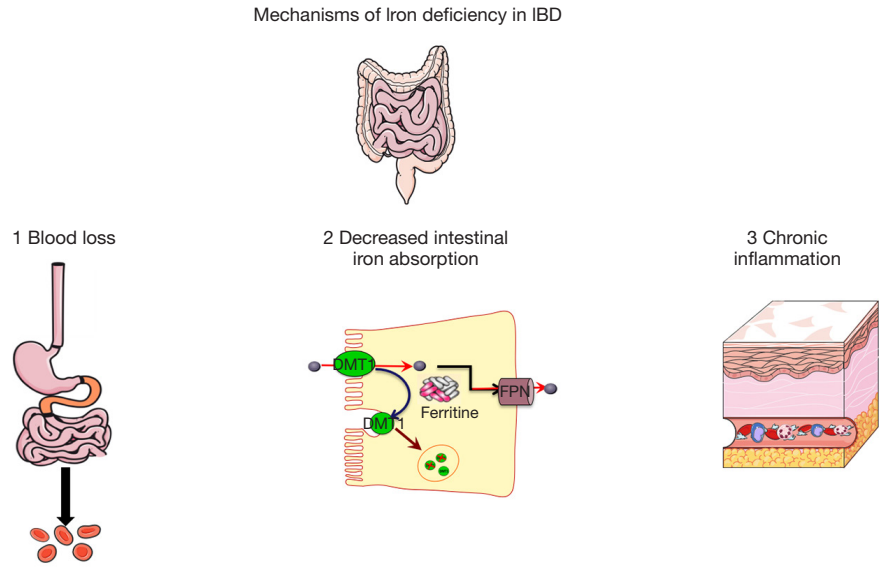

Figure 1 Schematic representation of the main aetiologies implied into the anemia observed in inflammatory bowel disease. The iron deficiency observed in IBD can lead to anemia and is generally a combination of absolute and functional deficiencies. The functional deficiency results from the pro-inflammatory climate leading to an unadapted overexpression of the main iron systemic regulator hepcidin.

patients with IBD are anemic, and 20–54% were shown to be deficient in iron (22). In UC, the prevalence was estimated at 66% in inpatients (23) and 40% in reference centers (24).

Several factors contribute to iron deficiency and anemia, including intestinal blood loss (macroscopic or microscopic), insufficient iron intake, reduced iron absorption, altered iron metabolism and storage, and the inhibitory effect of pro-inflammatory cytokines on erythropoiesis and iron-binding (25,26), as presented in *Figure 1*. Anemia related to chronic inflammation and iron deficiency anemia are the two most common causes of anemia in patients with IBD.

In a prospective study of patients with IBD, Jelsness-Jørgensen *et al.* showed that anemia was associated with chronic fatigue for at least six months (27).

Diagnosis of iron deficiency in IBD

The consensus published in 2015 on anemia management in IBD mentioned the following assays: complete blood count (because of diagnosis and classification of anemia), serum ferritin, and C-reactive protein to detect inflammation (28). The determination of iron deficiency anemia in patients with IBD is complicated: chronic inflammation with or without functional iron deficiency can overlap. Chronic inflammation can impact the values of iron metabolism proteins, as these are also acute-phase proteins. Serum ferritin is the most common biological exam to evaluate iron storage. Its primary disadvantage is that it is an acute-phase protein that can be increased in the setting of inflammation.

Absolute ID is characterized by a low blood ferritin concentration and a low transferrin saturation (TSAT) index. Opposingly, functional iron deficiency is characterized by a normal-to-high serum ferritin concentration and a low TSAT (29). Iron is mainly stored in the body as ferritin in the liver. The serum iron, bound to transferrin, is present in the blood circulation, resulting in release from macrophages and RBC lysis. TSAT (%) is the ratio of serum iron concentration (µmol/L)/total iron-binding capacity, TIBC; (µmol/L), after deduction of the serum concentration of transferrin (g/L). TSAT is considered the best indicator of iron reserves in the bone marrow, and a percentage below 16% confirms iron-deficient anemia (29). It should be mentioned that circadian changes in iron concentration cause fluctuations in TSAT and transferrin synthesis (30).

During inflammation, the lower limit of serum ferritin consistent with regular iron stores is generally assumed to be 100 µg/L. In this setting, the diagnostic criterium is serum ferritin less than 100 µg/L and transferrin saturation less than 20 percent. If the serum ferritin concentration is between 30 and 100 µg/L, a combination of true iron deficiency and functional iron deficiency is likely (18).

Thus, in IBD, ferritin measurement must be associated with the TSAT since inflammation led to a functional iron deficiency. Indeed, increases in hepcidin concentrations are induced by inflammatory cytokines, especially interleukin 6 (31,32).

In an unclear pattern, the soluble transferrin receptor (sTfR), a soluble monomer whose concentration could be measured in the blood (33). This truncated form circulates and forms complexes with transferrin. sTfR concentration is proportional to that of the transferrin receptor on erythropoietic cells. The level of sTfR is decreased during decreased erythropoietic activity. On the contrary, soluble TfR concentrations increased when erythropoiesis is enhanced, for instance, by hemolysis or ineffective erythropoiesis (34).

sTfR has the advantage of being insensitive to inflammation in contrast to ferritin (positive inflammation protein) and transferrin (negative inflammation protein) and entirely independent from hepatic function. Blood sTfR increases in proportion to iron requirements, depletion of iron stores, and increased transferrin synthesis by erythropoietic cells. To better evaluate body iron supplies, it has been proposed to report ferritin's value, particularly in logarithmic form: sTfR/log (ferritin). This ratio should be very high in iron deficiency by increased sTfR and decreased ferritin. This ratio has been proposed to be more sensitive than the sTfR alone and to reflect both the iron pool and the iron storage (35-37).

Zinc protoporphyrin (ZnPP) in circulating erythrocytes has historically been used as a marker of iron deficiency. In the last step of the heme biosynthesis, protoporphyrin IX is combined with Fe^{2+} to constitute the heme molecule (38). In the case of iron deficiency, Zn^{2+} replaces Fe^{2+} to produce ZnPP. The standard ratio of iron to zinc in protoporphyrin is approximately around 30,000:1, but ZnPP will increase to measurable concentrations with progressive iron deficiency. ZnPP production is unaffected by chronic inflammation and is a helpful indicator of iron deficiency in chronic inflammatory disease. ZnPP/heme ration <40 µmol/mol is a common value in the general population. ZnPP range between 40–80 µmol/mol heme represents latent iron deficiency (normal hemoglobin level), and values >80 µmol/mol heme are associated with manifest iron deficiency (39).

General consideration for the treatment of iron deficiency in IBD

Dietary iron is available either in hemic and non-hemic-forms. Heme iron form as hemoglobin contains ferrous ion Fe^{2+} in complex with protoporphyrin ring. Its absorption by enterocytes is higher, although this form is less represented in the food than the non-hemic form. Most iron in the diet is inorganic (Fe^{3+} or ferric ion) from plant-source foods. Organic iron constitutes 10–15% of total iron ingestion, but it represents more than 30% of the total absorbed iron (33) because of its higher bioavailability.

Anti-inflammatory therapy could help resolve the iron sequestration and could be helpful in the management of functional iron deficiency; anemia may, however, be back fast after successful treatment, due notably to absolute ID. Iron absorption has been shown to correlate with inflammation in a recent study (40).

Oral iron supplementation may potentiate gastrointestinal side effects; moreover, the malabsorption of oral iron is also suspected. Consequently, intravenous administration of iron is the first-line treatment in patients with clinically active IBD, intolerance to oral iron, or hemoglobin concentration less than 10 g/dL. IV iron is active, shows a faster response, and is better tolerated than oral iron in these patients (28).

Conclusion

The prevalence of ID, either absolute or functional, appears relatively high in IBD patients. Due to the inflammatory climate, this disease has to be accurately diagnosed, using TSAT rather than ferritin, and to be treated appropriately. Peyrin-Biroulet *et al.* proposed a three-step strategy (early detection and intervention, treating-to-target, and tight monitoring) to the management of iron deficiency in IBD patients (10). This management could be a way to easily and quickly improve the quality of life and, notably, fatigue in IBD patients.

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