REVIEW ARTICLE

Iron status in chronic inflammatory disease: therapeutic implications

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ABSTRACT

Anemia of inflammation (AI) is a very frequent clinical condition affecting globally more than a billion people with chronic inflammatory disorders, such as chronic kidney disease, heart failure, and inflammatory bowel disease. It is usually associated with iron deficiency (ID), which imposes a severe additional burden on the recovery from the primary disease. The pathophysiology of iron dysregulation that may ultimately lead to absolute iron deficiency anemia (IDA) during inflammation is multifactorial and includes reduced iron absorption in the bowel, iron retention in macrophages of the reticuloendothelial system, reduction in circulatory half-life of erythrocytes, inadequate production and activity of erythropoietin, and impaired proliferation and differentiation of erythroid progenitor cells. These result in hypoferremia and iron-restricted erythropoiesis. AI is mostly mild to moderate, normochromic and normocytic with normal or even increased ferritin levels. The current treatment options for AI include iron replacement therapy, treatment with erythropoiesis-stimulating agents, and red blood cell transfusion. ID management is based on oral or intravenous iron preparations. Given the pathophysiology, treatment with oral iron, although widely used, presents several limitations that impact its effectiveness in patients with chronic inflammatory conditions. Instead, intravenous iron preparations are a valuable option for patients with chronic inflammatory diseases, as they overcome reduced bowel absorption. Novel therapeutic approaches include downregulation of hepcidin synthesis and function, and stabilization of the hypoxia-inducible factor via inhibition of prolyl hydroxylase domain. Several studies in vitro and in vivo are ongoing; however, the results in humans are still elusive.

Introduction Patients with chronic inflammatory disorders, autoimmune diseases, and infections often present with anemia, namely anemia of inflammation (AI). The condition is usually associated with iron deficiency (ID), which makes the recovery process from the primary disease increasingly difficult.[1,2] ID is estimated to affect 37% to 61% of patients with chronic heart failure (CHF), 24% to 85% of patients with chronic kidney disease (CKD), and 13% to 90% of patients with inflammatory bowel disease (IBD).[3-5] The pathophysiology of iron dysregulation that may lead to iron deficiency anemia (IDA) during inflammation is multifactorial. It includes reduced iron absorption in the bowel, iron retention in macrophages of the reticuloendothelial system, reduction in a circulatory half-life of erythrocytes, inadequate production and activity of erythropoietin (EPO), and impaired proliferation and differentiation of erythroid progenitor cells.[1] Its occurrence is associated with progression and severity of the underlying disease, decreased quality of life (QoL), reduced cardiovascular performance, and adverse outcomes.[6,7] ID is a clinical condition per se, distinct from anemia, and defined as "a health-related condition in which iron availability is insufficient to meet the body's needs, and which can be present with or without anemia."[2] Recent clinical observations of inflammatory disorders have reported an association between reduced morbidity or mortality and the treatment of ID, even outside the context of anemia.[8] The major concerns among physicians are how to diagnose ID in patients with chronic inflammatory conditions, partially because of symptoms overlapping with

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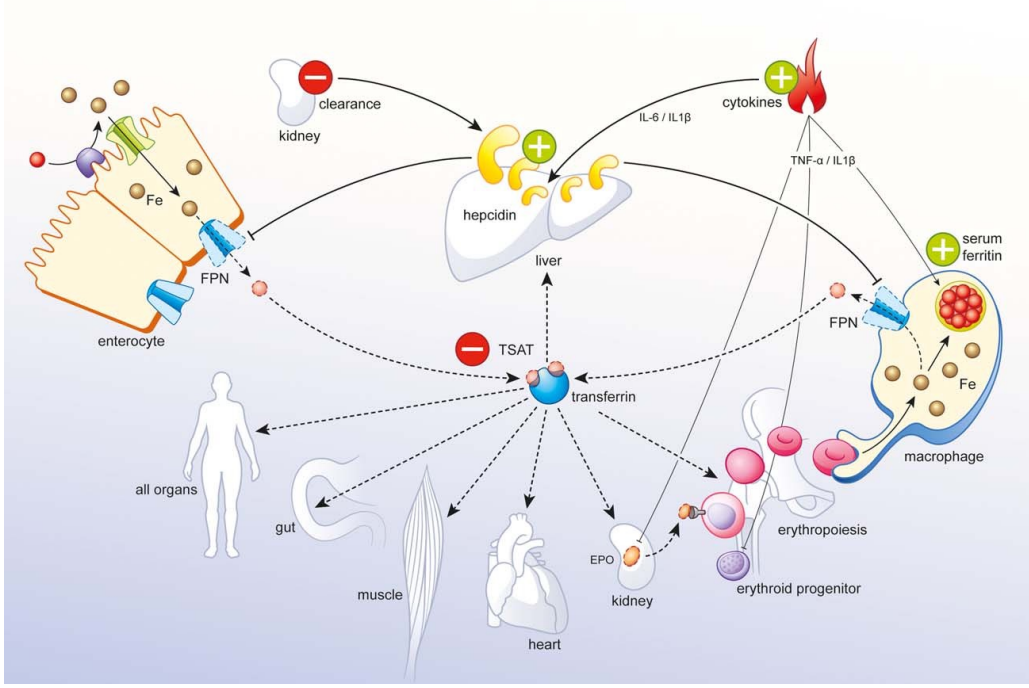

FIGURE 1 Pathophysiology of iron deficiency in chronic inflammation. Increased cytokine levels in inflammatory conditions enhance hepcidin synthesis. High hepcidin levels result in binding, internalizing, and degrading of ferroportin on the lateral membrane of duodenal enterocytes and spleen macrophages. Iron remains trapped in enterocytes and macrophages. This results in limited iron availability for hemoglobin production, which is referred to as iron-restricted erythropoiesis. From Cappellini et al[2]
Abbreviations: EPO, erythropoietin; FPN, ferroportin; IL, interleukin; TNF-α, tumor necrosis factor α; TSAT, transferrin saturation

the underlying disease and unclear laboratory diagnostic thresholds, particularly for ferritin.[9-12]

Mechanisms of iron deficiency in chronic inflammation Iron (Fe) is an essential element involved in a variety of vital functions, including oxygen transport, DNA synthesis, metabolic energy generation, and cellular respiration.[13] Iron homeostasis is the result of balanced cooperation between functional compartments (erythroid and proliferating cells), uptake and recycling systems (enterocytes and splenic macrophages), storage cells (hepatocytes), and mobilization processes.[13] The largest of these iron compartments is the erythron (erythrocytes and their precursors), which contains approximately two-thirds of iron almost exclusively accumulated in hemoglobin.[14] Hepatocytes are the storage compartment in which up to 1 g of iron is contained in the cytoplasmic ferritin.[14] The storage compartment could be depleted in the case of ID.[14] The plasma iron pool is only 3–4 mg, and it must turn over several times daily to meet the high (20–25 mg) demand of erythropoiesis and other tissues.[14] The iron carrier transferrin is central to iron trafficking.[14] Binding to its ubiquitous receptor TFR1, transferrin delivers iron to cells through the well-known endosomal cycle.[14] Most iron (20–25 mg/daily) is recycled by macrophages during phagocytosis of erythrocytes.[14] In humans, there is no regulated excretion of iron; thus, the iron balance is primarily controlled at the level of intestinal absorption, which takes place in the proximal section of the duodenum.[14] Under physiological conditions, intestinal iron absorption is controlled primarily by body iron content and erythropoiesis.[15] Specifically, iron uptake can be enhanced in the case of higher erythropoietic demand, or suppressed when iron stores are repleted.[16] The hepatic peptide hormone, hepcidin (encoded by the *HAMP* gene), and its transmembrane receptor, ferroportin (FPN), control the principal routes of iron transport and availability in the body.[17] Bone morphogenetic protein 6 (BMP6), a member of the tumor growth factor β family, is the most potent inducer of hepcidin production, and it is expressed in the liver in response to iron overload.[7] It binds to BMP receptor type 1 together with a co-receptor hemojuvelin, thus upregulating *HAMP* expression via SMAD1/5/8 signaling.[7] Inflammation induces functional iron deficiency, where total body iron levels are largely unchanged but iron is redistributed into macrophages. Inflammation through BMP6 increases the synthesis of hepcidin, which subsequently reduces FPN expression, resulting in macrophage iron retention, reduced dietary iron absorption, and finally development of hypoferremia. The result is a restricted iron supply for erythropoiesis responsible for progressive development of AI.[18,19] However, a prolonged inflammatory status may lead to concomitant absolute ID, because of persistently reduced iron absorption in the bowel. Inflammation-driven iron retention in macrophages is considered to represent

an innate immune mechanism in vertebrates, also known as "nutritional immunity."[1] It limits iron availability for the proliferation and pathogenicity of extracellular microorganisms.[1,20-22] FPN, which is the only known iron exporter, is expressed in cell types with an iron export function, such as macrophages, duodenal enterocytes, and hepatocytes. During inflammation, cell surface expression of FPN is reduced in transcriptional and post-translational mechanisms.[1] Increased hepcidin synthesis is the main mechanism inducing internalization and degradation of FPN and subsequent iron cellular retention, however, a second mechanism for inhibiting iron export via FPN and inducing hypoferremia is the direct transcriptional repression of FPN by proinflammatory cytokines and bacterial components in macrophages and hepatocytes. Inflammation-mediated transcriptional downregulation of FPN alone can be sufficient to cause hypoferremia and eventually AI in the absence of hepcidin activation.[23-25] ID, either functional or absolute, may contribute to several symptoms that can manifest even in the absence of progression to anemia. This is particularly relevant in different conditions characterized by inflammation, where some symptoms of the underlying disease may overlap with nonspecific ID symptoms, such as fatigue and reduced exercise tolerance. This means that physicians and patients do not always recognize the presence of ID and, as a consequence, diagnosis is not pursued and the condition is left untreated.[2]

Diagnosis of anemia of inflammation Iron-restricted erythropoiesis is the pathophysiological mechanism of AI and iron deficiency anemia (IDA). Both conditions may coexist in patients affected by inflammatory diseases. Iron restriction in AI mainly originates from iron retention in macrophages and, only to a minor extent, from reduced dietary iron absorption.[26] This status is referred to as functional ID and is hallmarked by iron storage in macrophages. On the contrary, in IDA there is an absolute ID that occurs because of the imbalance between iron uptake, iron utilization, and iron loss. AI usually presents as normocytic, normochromic, mild to moderate anemia with decreased serum iron concentrations and reduced transferrin levels.[12] As transferrin synthesis is suppressed under inflammatory conditions, transferrin saturation may appear normal. Therefore, the widely used transferrin saturation threshold of 20% often fails to detect patients with pathophysiological AI being the consequence of inflammation-driven transferrin suppression.[27] AI is characterized by increased levels of inflammatory markers, such as interleukin 6 and C-reactive protein, accompanied by a normal or increased level of ferritin owing to macrophage iron accumulation, whereas in IDA ferritin levels are decreased. The main diagnostic challenge is identification of true ID in patients with AI, as they need further specific diagnostics to evaluate the source of IDA and different treatment than the patients suffering from AI alone.[2] Several biomarkers, alone or in combination, were studied to detect true ID in inflammation. An early and sensitive biomarker for erythropoiesis is reticulocyte hemoglobin content, which is a reliable indicator of IDA not influenced by inflammation.[7] Serum concentrations of soluble transferrin receptor (sTFR) are elevated in patients with ID, as a sign of increased iron requirement by erythroid progenitor cells. Although sTFR was shown to be a good diagnostic biomarker for differentiating between ID and IDA, there is still some overlap. Calculation of the sTFR/log ferritin ratio, known as a ferritin index, seems to be a better parameter to detect depleted iron stores, also in patients with signs of inflammation. Currently, the ferritin index above 2 defines patients with both AI and IDA, while the ferritin index below 1 defines mainly patients with AI, although some overlap may exist.[28] Hepcidin, although extensively studied in chronic inflammation, is not practically used for diagnostic purposes. Some classical hematologic parameters, such as mean corpuscular volume or mean hemoglobin content of erythrocytes, the latter being reduced in anemia of chronic disease and true ID, may help in making the right diagnosis.[7] A review of international guidelines available for CHF, CKD, and IBD reveals no consensus practical guidance for diagnosing ID independently of anemia.[2]

Iron deficiency and anemia of inflammation in some chronic inflammatory diseases In the following sections we outline the role of ID in patients with CHF, CKD, and IBD, as well as the associated clinical outcomes that further prompt its diagnosis and management.

Iron deficiency in chronic heart failure ID is estimated to affect between 37% and 61% of patients with CHF, and its prevalence increases as CHF advances.[3] The etiology of ID in CHF is thought to be multifactorial, including insufficient nutrition, decreased gastrointestinal iron absorption, increased gastrointestinal blood loss that may occur partially as a result of antiplatelet and anticoagulant drugs, and importantly, it is a consequence of the chronic inflammatory state of these patients.[29] Increased hepcidin levels and markers of inflammation are observed in the patients with more advanced CHF. Regular evaluation of iron status and treatment of possible ID is recommended by current guidelines.[30] The increased risk of mortality from ID in the studies evaluating CHF patients ranges between 40% and 60%.[2] ID in CHF has also been associated with increased frequency of hospitalizations, with 1 study showing that the risk of hospitalization doubled in patients who were not treated for ID, as compared with those who received the therapy (relative risk [RR], 2.23; 95% CI, 1.59–3.42; $P < 0.01$).[2] It has been reported in several studies that intravenous iron supplementation can improve clinical parameters and the prognosis of CHF.[31,32]

Notably, the benefit from treating ID in this setting is observed whether or not the patients are also anemic, thus establishing ID as an independent therapeutic target in CHF.[2] This has led to including ID screening into the diagnostic workup of the patients with CHF, and recommended treatment with intravenous iron (eg, ferric carboxymaltose).[33,34]

Iron deficiency in chronic kidney disease The prevalence of ID in patients with CKD has been reported to range from 24% to 85% in different cohorts, and it increases upon CKD progression.[35] Similarly to CHF, iron deficiency in CKD can arise from decreased gastrointestinal iron absorption, malnutrition, and blood loss. The use of erythropoiesis--stimulating agents (ESAs) in CKD, while effective in correcting anemia, can further exacerbate ID, which in turn may result in poor response to ESAs.[36] Hepcidin levels in patients with CKD are elevated by different mechanisms. Reduced renal EPO secretion induces erythroferrone (ERFE) in erythroid progenitors, enhancing iron availability for erythropoiesis by suppressing hepcidin expression. In the patients with CKD who are anemic, there is a positive correlation between serum EPO and ERFE levels, although hepcidin levels vary between different cohorts, being also affected by hypoxia and anemia-inducible factors, such as platelet-derived growth factor BB, growth-differentiation factor 15, or sexual hormones.[37,38] Moreover, increased hepcidin levels are further aggravated by concomitant inflammation often linked to the underlying disease or dialysis. Recently, fibroblast growth factor 23 (FGF23) has been implicated in the development of AI in CKD. Kidney damage decreases the expression of the renal FGF23 coreceptor α-Klotho, thereby reducing the FGF23 response, however, to maintain mineral homeostasis, FGF23 levels increase. Elevated FGF23 levels, which also occur in response to ID and inflammation, affect hematopoietic stem cell differentiation and EPO regulation. Anemia in CKD is frequently associated with reduced QoL, particularly in physical domains, such as vitality and energy. Several observations support the advantages, in terms of clinical progression and outcome, of treating ID prior to anemia development and requirement for ESAs in CKD patients. Anemia in CKD patients is usually treated with a combination of iron supplementation and ESAs, which improves hemoglobin levels and QoL. Nevertheless, some patients remain poor responders.[39]

Iron deficiency in inflammatory bowel disease ID affects between 13% and 90% of patients with IBD, depending on the population studied, with an active or quiescent disease. IBDs are conditions of cytokine-driven chronic gastrointestinal inflammation of multifactorial etiopathogenesis. IDA is recognized as one of the most common complications and extra-intestinal manifestations of IBD. However, over 50% of patients diagnosed with IDA remain untreated.[40] Several mechanisms contribute to ID and anemia in the patients with IBD, and they include: 1) malnutrition (including iron) due to impaired intestinal absorption, 2) medication-associated toxicity (eg, azathioprine and methotrexate), 3) surgical procedures (eg, extensive bowel resection), 4) chronic intestinal bleeding from disease-associated ulcerations, and 5) inflammation.[41] Interestingly, the damaged enterocytes in response to inflammation and / or hypoxia affect the intestinal microbiome by reducing duodenal iron absorption. Notably, improvements in iron status with intravenous iron treatment have led to significantly better QoL in patients with ulcerative colitis and Crohn disease, according to IBD QoL questionnaire scores (P <0.001) and SF-36 physical (P <0.001) and mental component (P = 0.024) scores.[42]

Other conditions characterized by inflammation, such as autoimmune diseases, cancer, chronic lung diseases, or infectious diseases may present with ID or even IDA that are often disregarded as a problem in clinical practice, even though some data support improvement of the clinical outcome in such conditions, if ID treatment is implemented.[1]

Current treatment options for anemia of inflammation The most effective treatment for AI is to cure the underlying disease and the resolution of inflammation. In some cases with very mild ID or mild anemia not affecting the patient's QoL, specific treatment could be temporarily omitted but this should be evaluated on a patient-by-patient basis.[1,2,8,12] The current treatment options for AI include iron replacement therapy, treatment with ESAs, and red blood cell transfusion. ID treatment is based on oral or intravenous iron preparations.[43] There are advantages and limitations of each, and physicians must decide on the most suitable option for their patients. Several factors should be considered when selecting the best option including the inflammatory condition of the patient, the degree of iron deficit (ie, the total amount of iron to be replenished), and the time frame for achieving the replacement of iron stores. Oral iron treatments are convenient and the most widely used, however, several limitations impact their effectiveness in patients with chronic inflammatory conditions. Inflammation (even low-grade inflammation) impairs intestinal iron absorption due to internalization of hepcidin-related FPN, making oral iron supplementation ineffective.[44] Moreover, oral iron treatment has recently been associated with significant changes in the normal gut microbiota, explaining why oral iron increases the well known gastrointestinal intolerance profile, which is particularly detrimental to IBD patients. Therefore, parenteral intravenous iron administration is the potential optimal option of iron supplementation in patients with chronic (inflammatory) diseases.[45] The intravenous iron treatment replenishes iron stores more rapidly than oral treatment and it allows for avoiding the risk of gastrointestinal

side effects. Many guidelines acknowledge the benefits of intravenous iron preparations as a valuable option for patients with chronic inflammatory diseases, mainly those who are nonresponsive to, noncompliant with, or intolerant to oral iron treatment, as well as those who have severe ID and require rapid replenishment of iron and increase of hemoglobin level. There are several intravenous iron preparations with variable dosing, infusion times, efficacy, and safety profiles.[46] Despite the benefits of intravenous iron administration, there is, although rare, a risk for serious, life-threatening hypersensitivity reactions that need an emergency intervention. Ferric carboxymaltose has been widely studied in various chronic inflammatory conditions, resulting in substantial evidence that supports its effectiveness and good tolerability across patient groups. A potential side effect of ferric carboxymaltose and of ferric derisomaltose is moderate to severe hypophosphatemia (<2 mg/dl), probably due to increased expression of FGF23, which increases urinary phosphate excretion and inhibits 1-α hydroxylase and thus vitamin D activation.[47] Treatment with recombinant human ESAs is a widely used therapy for AI, especially in patients with CKD or cancer. These drugs counteract the antiproliferative effects of proinflammatory cytokines and stimulate iron uptake and heme biosynthesis in erythroid precursors.[47,49] However, ESAs were associated with unfavorable clinical outcomes, particularly in patients with an initially poor response.[1] Red blood cell transfusions are restricted to patients with severe anemia (hemoglobin, <8 g/dl) and are only a temporary strategy due to increased mortality in specific conditions.[1] Although iron supplementation remains the first line therapy for the patients with AI and concomitant IDA, new treatment strategies are under development. Mobilization of stored iron from macrophages of the reticuloendothelial system is probably more suitable than repeated iron supplementation.[1]

Novel therapeutic approaches Growing knowledge of the pathophysiology underlying AI encouraged development of novel therapeutic strategies. There are 2 main approaches to rearrange the body iron stores and to correct the iron restricted erythropoiesis that characterizes AI: 1) to downregulate hepcidin synthesis and function, and 2) to stabilize the hypoxia inducible factor (HIF) via inhibition of prolyl hydroxylase domain.[1] Several in vitro and in vivo studies have been targeting hepcidin synthesis directly or indirectly, however, the results in humans are still elusive.[50,51] The efficacy of hypoxia-inducible factor prolyl hydroxylases inhibitors (HIF-PHIs) has been shown to ameliorate anemia in CKD, however, these drugs have not been licensed for clinical use by Food and Drug Administration (FDA), whereas they were approved by the European authorities (European Medicines Agency). The FDA justified its decision by the fact that HIF-PHIs activate numerous HIF target genes in various organs.[1] Specific concerns include higher frequency of thromboembolic events, acceleration of diabetic retinopathy, or progression of malignancy in some patients treated with HIF-PHIs.[52-54]

ARTICLE INFORMATION

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