REVIEW ARTICLE

Iron Deficiency in Heart Failure: Unveiling the Hidden Culprit

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ABSTRACT

Iron deficiency (ID) is a frequent comorbidity in patients with heart failure (HF). Coexistent HF and ID make the issues more challenging to diagnose and treat. Iron deficiency exacerbates clinical symptoms, impairs quality of life and increases the risk of recurrent hospitalization for HF. Conversely, a proinflammatory state and altered gut kinetic in HF may result in absolute or functional ID, which conventional laboratory makers may not diagnose and differentiate accurately. Novel diagnostic markers like soluble transferrin receptor (sTfR), reticulocyte hemoglobin concentration, red blood cell distribution width, sTfR: log (ferritin) ratio and serum hepcidin levels may help to diagnose ID more accurately in the setting of HF. The intravenous (IV) iron formulation has shown promising results in improving the functional class and reducing recurrent hospitalization in patients with HF and ID. Futuristic therapies like nanosized iron preparations, hepcidin inhibitors and hepcidin antagonists may help manage ID more efficiently and conveniently in HF. This manuscript explores the relationship between ID and HF. It also provides the latest information related to the diagnosis and treatment of ID in HF patients.

Keywords: Iron deficiency, heart failure, intravenous iron formulation

Iron is essential to executing several physiological processes, such as oxygen transport and storage, cellular respiration, energy metabolism, and control of vascular tone[1]. Like all other chronic inflammatory diseases, iron deficiency (ID) frequently afflicts patients with heart failure (HF). ID is a common comorbidity in patients with HF, affecting up to 50% of all ambulatory patients[2]. Prevalence varies depending on the criteria used to diagnose ID in the cohort analyzed[3]. ID is associated with worsening of the signs and symptoms of HF, poor quality of life, and increased risk of recurrent hospitalization and death[4]. Strategies targeting ID in the HF cohort significantly improve clinical outcomes, New York Heart Association (NYHA) functional class, exercise capacity, and quality of life[5-10].

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IRON HOMEOSTASIS

Iron is vital for the human body. In free form, iron causes oxidative injury and may lead to premature cell death. Iron, therefore, must remain bound to protein to ensure safety and stability. Iron is stored as an iron-protein complex in the liver, spleen, and reticuloendothelial cells (storage pool). In the bloodstream, it is transported conjugated with apo-transferrin as transferrin. Transferrin carries iron around the body, which is physiologically usable by cells after uptake by transferrin receptor-1 (functional pool). Three key regulators are crucial in iron homeostasis. Ferroportin regulates iron absorption from the gut and its discharge from the stored pool. Hepcidin induces internalization and degradation of ferroportin and acts as a master regulator of iron metabolism. Lastly, erythroferrone is a negative regulator of iron metabolism. It inhibits hepcidin production, thus ensuring iron availability for erythropoiesis[11-13]. All these proteins work in a coordinated manner to maintain a stable level of iron in the body.

EFFECT OF HF ON IRON HOMEOSTASIS

Heart failure is a proinflammatory condition. It is associated with elevated levels of inflammatory cytokines, which result in elevated hepcidin levels. Hepcidin negatively interacts with ferroportin, hindering iron

absorption from the gut and its release from the storage pool. In this way, patients with HF are at risk of both absolute (depleted iron stores) and functional ID (sufficient iron not available at the cellular level despite normal total body iron)[13]. Within the framework of HF, many other factors may precipitate the state of ID (Table 1). Some of these factors include nutritional deficiency, poor bioavailability of dietary iron, edematous gut, blood loss secondary to antiplatelet or anticoagulant medication and associated comorbidities[2].

EFFECT OF IRON DEFICIENCY ON HF OUTCOMES

Iron is crucial for synthesizing hemoglobin, myoglobin, cytochrome *c*, and many other proteins. It acts as a cofactor of several enzymes, including nitric oxide synthase. ID, therefore, has a deleterious effect on oxygen transportation (hemoglobin) and aerobic respiration of muscles (myoglobin), oxidative phosphorylation (cytochrome *c*), and other processes dependent on a sufficient level of iron (Table 2)[1,13]. Patients with HF and ID exhibit a high prevalence of anemia, adverse remodeling, and worse muscular symptoms (such as muscle pain, fatigue, cramps, shortness of breath, and poor exercise capacity) secondary to insufficient heme production. ID disturbs oxidative phosphorylation and reduces adenosine triphosphate (ATP) production. Therefore, tissues with higher energy requirements (such as the myocardium, skeletal muscle, and the central nervous system) are affected most by ID. Lastly, ID disrupts the production of nitric oxide synthase (NOS), resulting in vasoconstriction. This, in turn, worsens symptoms like difficulty breathing and fatigue, which also result in recurrent hospitalization[1,13].

DEFINING IRON DEFICIENCY IN HEART FAILURE

Iron deficiency in HF can be absolute iron deficiency (AID) or functional iron deficiency (FID). In AID iron, the total body stores of iron get depleted. Conversely, FID typifies a situation where iron stores are normal or elevated (Table 3)[14-16]. However, the downregulation of ferroportin and upregulation of hepcidin and other inflammatory cytokines hinder iron mobilization from the storage pool. Ferritin levels (reflection of storage pool) and transferrin saturation (reflection of iron bioavailability) are the two most commonly used laboratory parameters to define ID in routine clinical settings (Fig. 1). Serum ferritin <30 µg/L and transferrin saturation (TSAT) <16% suggest a state of ID[14]. However, considering the effect of HF on serum ferritin and TSAT, it is imperative to change the criterion of diagnosing ID in the setting of HF. Serum ferritin is an acute phase

Table 1. Fundamental Causes of Iron Deficiency in Heart Failure

Poor absorption due to increased gut thickness
Poor absorption due to gut edema
Poor bioavailability of dietary iron
Blood loss due to antiplatelets or anticoagulants
Associated comorbidities
Elevated hepcidin levels
Elevated inflammatory cytokines

Table 2. Critical Substrates Affected by Iron Deficiency[1,13]

Substrate	Essential role	Impact of ID on patients with HF
Hemoglobin	Oxygen transportation	Anemia, adverse remodeling of the left ventricle, fatigue, shortness of breath, recurrent hospitalization, increased cardiovascular death.
Myoglobin	Oxygen storage in skeletal muscle	Muscle pain, fatigue, cramps, shortness of breath, and poor exercise capacity.
Cytochrome *c*	Electron transport chain for ATP generation	Adverse impact on tissues with higher energy requirements such as the myocardium, skeletal muscle, and the central nervous system.
Nitric oxide synthase	Control of vascular tone	Worsens symptoms like difficulty breathing, fatigue, and recurrent hospitalization.

Table 3. Absolute and Functional Iron Deficiency in Heart Failure[14-16]

Absolute iron deficiency

- Depletion of both storage and functional pool of iron.
- Diagnosed as serum ferritin (a marker of storage pool) <100 µg/L and transferrin saturation (a marker of the functional pool) <20%.

Functional iron deficiency

- Normal or elevated storage pool but sequestration of the functional pool of iron.
- Diagnosed as serum ferritin (a marker of storage pool) 100-300 µg/L and transferrin saturation (a marker of the functional pool) <20%.

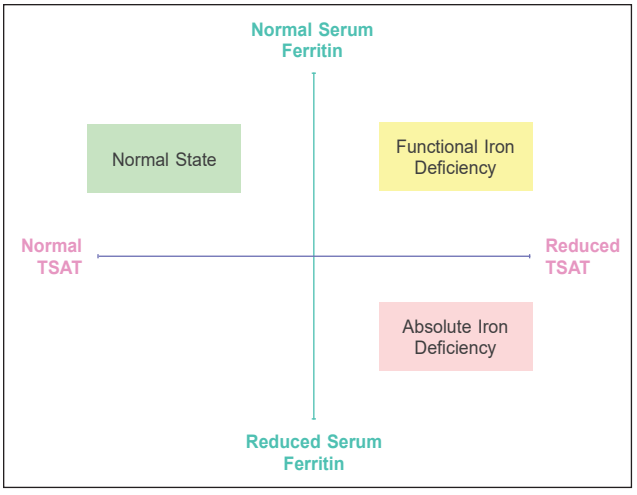

Figure 1. Absolute and functional iron deficiency in patients of heart failure. In AID, both iron storage and functional pools are depleted. However, in FID, the storage pool remains normal or even elevated, but the iron cannot move out of the storage pool. This may be due to the impact of the altered hepcidin-ferroportin axis in HF. This leads to improper iron availability to erythroid and nonerythroid tissue despite a regular storage pool.

reactant and gets nonspecifically elevated in conditions with activated inflammatory pathways such as HF. This change correlates with the extent of inflammation. Conversely, transferrin is a negative phase reactant and may get suppressed in HF[15].

Although there is no precise serum ferritin and TSAT cut-off, serum ferritin levels <100 μg/L or 100-300 μg/L if TSAT is <20% diagnose ID in HF with 82% sensitivity and 72% specificity[16]. Novel markers such as soluble transferrin receptor (sTfR), reticulocyte hemoglobin concentration, and red blood cell distribution width (RDW) can diagnose ID more accurately in patients with HF. However, these markers have yet to be routinely used. Additionally, measuring sTfR, sTfR: log (ferritin) ratio or hepcidin levels could be more effective in discriminating AID from FID[17]. A detailed description of all these investigations is beyond the scope of this manuscript.

MANAGEMENT OF IRON DEFICIENCY IN HEART FAILURE

Review of Literature

Clinical trials and meta-analyses have suggested beneficial effect of IV iron in patients with ID (Table 4)[5-10,18-20]. In the FAIR-HF (Ferinject Assessment in patient with IRon deficiency and chronic Heart Failure) trial, the use of IV ferric carboxymaltose in patients of HF

Table 4. Conclusion of Major Clinical Trials and Meta-analyses Related to the Role of Intravenous Iron Therapy in Patients with Heart Failure[5-10,18-20]

Study	Year	Conclusion
FAIR-HF[5]	2009	• Treatment with intravenous (IV) ferric carboxymaltose improves symptoms, functional capacity and quality of life in patients with chronic HF and ID, regardless of anemia. • IV ferric carboxymaltose has an acceptable side-effect profile.
CONFIRM-HF[6]	2015	• IV ferric carboxymaltose over 1 year in symptomatic iron deficient HF patients resulted in sustainable improvement in functional capacity, symptoms, and quality of life. • It may be associated with a risk reduction of hospitalization for worsening HF.
IRONOUT-HF[7]	2017	• High-dose oral iron over 16 weeks did not improve exercise capacity among participants with HF with reduced ejection fraction (HFrEF) with ID.
AFFIRM-AHF[8]	2020	• Treatment with IV ferric carboxymaltose in patients with left ventricular ejection fraction (LVEF) of <50%, ID and who were stabilized after an episode of acute HF resulted in reduced risk of HF hospitalizations. • There was no apparent effect on the risk of cardiovascular death.
IRONMAN[19]	2022	• In patients with HF, reduced LVEF, and ID, IV ferric derisomaltose administration was associated with a lower risk of hospital admissions for HF and cardiovascular death.
HEART-FID[18]	2023	• Ambulatory patients of HFrEF and ID, did not demonstrate any benefit in hierarchical composite of death, hospitalizations for HF, or 6-minute walk distance with IV ferric carboxymaltose.
Meta-analysis by Myint et al[20]	2022	• Patients with HF and ID demonstrated lower HF hospitalizations with IV iron therapy. • IV iron therapy improves the quality of life and decreases health care expenditure.
Meta-analysis by Graham et al[9]	2023	• In HF patients with ID, IV iron therapy reduces the risk of hospitalization for HF. • Its effect on cardiovascular or all-cause mortality remains inconclusive.
Meta-analysis by Salah et al[10]	2023	• IV iron therapy in patients with HF reduces the composite risk of first hospitalization for HF and cardiovascular mortality. • There was a reduction in first and recurrent hospitalizations for HF. • No effect on all-cause mortality or cardiovascular mortality.

with ID showed significant improvement in NYHA classification, functional capacity, and quality of live[5]. The results were similar in patients with anemia and without anemia. AFFIRM-AHF, a randomized, double-blind, placebo-controlled trial comparing the effect of IV ferric carboxymaltose on hospitalizations and mortality in iron deficient subjects admitted for acute HF, investigated the effect of IV ferric carboxymaltose on outcomes in patients who were stabilized after an episode of acute HF. Patients who received IV ferric carboxymaltose, showed a significant reduction in HF hospitalization compared to placebo (relative risk [RR], 0.74; 95% confidence interval [CI], 0.58-0.94) but no reduction in cardiovascular death[8]. IRONMAN (Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency) trial investigated the long-term safety and efficacy of IV ferric derisomaltose in a predominately outpatient HF population. Data suggested numerically lower HF hospitalizations and cardiovascular death in patients who received the ferric derisomaltose arm (22.4 per 100 patient-years) than in the placebo arm (27.5 per 100 patient-years). However, it failed to reach significance (p = 0.07)[19].

A meta-analysis conducted by Myint et al revealed a 13.8% decreased risk of HF hospitalizations (odds ratio [OR] 0.59; 0.35-0.98, p = 0.040) and a 17.5% reduction in the composite outcome of HF hospitalizations or cardiovascular mortality. All-cause and cardiovascular mortality were not different between IV iron and placebo groups[20].

Similar results were observed in a meta-analysis of 10 randomized controlled trials by Graham et al. It suggested a significant reduction in composite outcomes of recurrent hospitalizations for HF and cardiovascular mortality (rate ratio 0.75, 95% CI 0.61-0.93; p < 0.01) and first hospitalization for HF or cardiovascular death (OR 0.72, 95% CI 0.53-0.99; p = 0.04) in the group of patients who received IV iron as compared to those who received placebo or standard care. Similar to the prior meta-analysis, effects on cardiovascular (OR 0.86, 95% CI 0.70-1.05; p = 0.14) and all-cause mortality (OR 0.93, 95% CI 0.78-1.12; p = 0.47) were inconclusive[9].

Calculating Iron Deficit

Conventionally, the total iron deficit is estimated using the modified Ganzoni formula[21]. This equation estimates iron deficit by calculating iron attached to deficit hemoglobin. In healthy individuals, blood volume is 7% (0.07) of body weight. Iron content in hemoglobin is 0.34% (0.0034) g/dL. So, the total iron deficit in mg/L will be as below.

Iron deficit = weight (kg) × (target Hb - actual Hb) × 0.0034*0.07*10,000 + Depot iron.

Depot iron here represents an extra depot dose to replenish iron stores. This is usually kept at 500 mg. Notably, the above-mentioned formula may not accurately reflect the actual iron needs of the patient. It is crucial to consider other factors, such as inflammation, comorbidities and medication while estimating iron deficits in HF patients.

Selection of Iron Formulation

Oral iron formulations are not the preferred choice to treat ID in patients with HF. The IRONOUT HF (Iron Repletion effects ON Oxygen UpTake in Heart Failure) trial investigated the effects of oral iron therapy on exercise capacity and quality of life score in patients with HF with reduced ejection fraction and ID. Despite improvement in iron biomarkers such as transferrin saturation and ferritin levels, exercise capacity was not improved compared to placebo[7]. Unlike oral iron therapy, IV iron therapy benefits the 6-minute walk test distance, peak oxygen consumption, quality of life, and improvement in NYHA class[9]. IV iron formulations contain a core of iron hydroxide enveloped by variable carbohydrate complexes[22]. The carbohydrate envelope in the earlier formulation was composed of high molecular weight dextran. These formulations are no longer preferred due to the high risk of serious drug events associated with them[4]. Iron sucrose, ferric carboxymaltose, and ferric derisomaltose are the three most commonly studied nondextran IV iron formulations to treat ID in patients with HF (Table 5)[5,6,8,18,19,23,24]. Data from a recent meta-analysis demonstrated no significant difference in outcome

Table 5. Intravenous Iron Formulation Available for Management of Iron Deficiency in Heart Failure[5,6,8,18,19,23,24]

Formulation	Maximum dose (in single setting)	Duration of administration	Evidence in HF
Iron sucrose	200 mg	30 min	Toblli et al[23] FERRIC-HF[24]
Ferric carboxymaltose	1,000 mg	15 min	FAIR-HF[5], AFFIRM-AHF[8], HEART-FID[18], CONFIRM-HF[6]
Ferric derisomaltose	20 mg/kg up to 2,000 mg	20 min	IRONMAN[19]

Table 6. Clinical Guidelines for the Management of Iron Deficiency in Heart Failure

	European Society of Cardiology Guidelines	ACC/AHA Guideline
Recommendation of screening	All patients with HF (COR I; LOE C)	All patients with HF
Target population	Symptomatic patients with LVEF <45% (COR II; LOE A) Patients recently hospitalized for HF with LVEF <50% to reduce risk of hospitalization (COR II; LOE B)	Patients with HFrEF and ID (COR II; LOE A)
Treatment effect	Symptomatic patients with LVEF <45%: Alleviate HF symptoms, improve exercise capacity and QOL (COR II; LOE A) Symptomatic patients recently hospitalized for HF with LVEF <50%: Reduce the risk of hospitalization (COR II; LOE B)	Improve exercise capacity and QOL (COR II; LOE A)
Diagnosis	Serum ferritin <100 or Serum ferritin 100-300, if TSAT <20%	Serum ferritin <100 or Serum ferritin 100-300, if TSAT <20%
Management	Iron replacement with IV ferric carboxymaltose	IV iron replacement

between different IV iron-carbohydrate formulations when similar end points were measured[25].

Current Guidelines

Based on ample evidence, the 2021 European Society for Cardiology guidelines and the 2022 AHA/ACC/HFSA guidelines recommend using IV iron to improve functional status and quality of life in groups of patients with HF and ID (Table 6)[26,27].

FUTURE PROSPECTS

Novel markers and therapeutic options for managing ID are in the research spotlight. Newer diagnostic markers diagnose ID more accurately in the HF setting and can differentiate AID from FID. Some key diagnostic markers are sTfR, reticulocyte hemoglobin concentration, RDW, sTfR: log (ferritin) ratio, and serum hepcidin levels. sTfR levels increase in response to ID to absorb more iron. sTfR, therefore, may diagnose functional iron status more accurately than traditional markers.

Reticulocyte hemoglobin concentration represents iron available for new red blood cell production. Low levels of reticulocyte hemoglobin concentration are a clear sign of ID. RDW measures the red blood cell size variation. Higher RDW values suggest disrupted red cell production, which could indicate ID. sTfR: log (ferritin) ratio is another marker that helps distinguish FID from AID. Higher levels are consistent with FID. Lastly, the estimation of hepcidin levels helps to understand iron homeostasis. Hepcidin inhibits iron's release from body stores. Thus, elevated levels are consistent with FID[17].

Nanosized iron preparations are emerging oral iron therapies that may help to resolve concerns of poor absorption and gastrointestinal side effects related to traditional oral iron therapy[28].

Compounds that antagonize hepcidin or its effects could help ameliorate HF-associated ID and are in the research phase. The use of such compounds in clinical settings warrants further investigation and testing[29]. While more research is needed to fully understand the safety and efficacy of these newer therapeutic options, they represent exciting advances in cardiovascular medicine.

CONCLUSION

Iron deficiency is a frequent comorbidity in HF patients. HF adversely affects iron homeostasis, leading to states ranging from AID to FID. According to current guidelines, ID in HF is diagnosed using serum ferritin and transferrin. However, upcoming markers such as sTfR, reticulocyte hemoglobin concentration and RDW may help diagnose ID more accurately in patients with HF. Further, novel investigations such as sTfR, sTfR: log (ferritin) ratio, or hepcidin levels could more effectively discriminate AID from FID. Once diagnosed, nondextran IV iron therapy is safe and effective in improving functional class and quality of life in patients of ID with HF.

Although current therapy does not offer cardiovascular mortality benefits, innovative therapies (hepcidin inhibitor, nanoparticle and gene therapy) may be more effective for treating ID.

Key Messages of the Current Manuscript

- Iron deficiency worsens the clinical symptoms and functional class related to HF.
- Patients with HF may suffer from absolute or functional ID. These two conditions may happen independently or simultaneously.
- Serum ferritin and transferrin saturation can diagnose ID with modest sensitivity and specificity in the HF setting. Novel markers for a more accurate diagnosis of ID and distinguishing the two types are in the research phase.
- Nondextran IV iron formulation therapy is currently approved for managing ID in HF. Newer therapies like nanosized iron preparation and therapy targeting hepcidin are under clinical trials.

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Declaration of Generative AI and AI-assisted Technologies in the Writing Process

During the preparation of this work the authors used Grammarly AI tool in order to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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