IRON DEFICIENCY IN CARDIOVASCULAR DISEASE: BEYOND HEART FAILURE

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Abstract

Iron deficiency is a common but often underrecognized condition in cardiovascular disease. While its role in heart failure is well established, emerging evidence suggests broader clinical relevance across multiple cardiovascular conditions. This narrative review examines the pathophysiology, clinical impact, and therapeutic implications of iron deficiency beyond heart failure. Special attention is given to its role in coronary artery disease, atrial fibrillation, and perioperative cardiovascular risk.

Iron deficiency is associated with reduced exercise capacity, impaired myocardial energetics, and worse clinical outcomes. Intravenous iron therapy has demonstrated clinical benefits in selected populations, particularly in heart failure, while its role in other cardiovascular conditions is still evolving.

Recognizing and treating iron deficiency may represent an important step toward improving cardiovascular outcomes.

Keywords: *iron deficiency, cardiovascular disease, heart failure, ferritin, transferrin saturation, intravenous iron*

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METHODS

Aim

To evaluate the role of iron deficiency in cardiovascular disease beyond heart failure and its clinical implications.

Design: Narrative literature review focused on clinically relevant evidence.

Data sources: PubMed, Scopus, Web of Science

Timeframe: 2015–2025

Search terms: “iron deficiency”, “cardiovascular disease”, “heart failure”, “coronary artery disease”, “ferritin”, “transferrin saturation”, “intravenous iron”

Inclusion criteria:

- randomized clinical trials
- meta-analyses
- observational studies
- guideline documents

Scope: Included: **15 key sources**

1. Introduction

Iron deficiency is one of the most common nutritional deficiencies worldwide and is increasingly recognized as an important factor in cardiovascular disease. Traditionally, it has been associated primarily with anemia, but recent evidence shows that iron deficiency itself, even in the absence of anemia, has significant clinical consequences [1].

In cardiology, the role of iron deficiency has been most extensively studied in heart failure, where it is associated with reduced exercise capacity, impaired quality of life, and increased risk of hospitalization. However, its impact extends beyond heart failure and may influence a wide range of cardiovascular conditions. Iron plays a central role in cellular energy metabolism, mitochondrial function, and oxygen transport. Deficiency leads to impaired myocardial energetics and reduced skeletal muscle performance, which are critical determinants of functional capacity in cardiovascular patients.

Despite its clinical relevance, iron deficiency is often underdiagnosed. This is partly due to the complexity of its definition in the setting of chronic disease, where traditional markers such as ferritin may be influenced by inflammation. The aim of this review is to explore the broader role of iron

deficiency in cardiovascular disease and to evaluate its potential as a therapeutic target beyond heart failure.

2. Definition and Diagnosis of Iron Deficiency in Cardiovascular Disease

The diagnosis of iron deficiency in cardiovascular patients differs from that in the general population due to the presence of chronic inflammation and comorbid conditions. In this setting, standard markers of iron status must be interpreted with caution. Iron deficiency is broadly classified into two types: absolute and functional. Absolute iron deficiency reflects depletion of total body iron stores, typically due to inadequate intake, chronic blood loss, or malabsorption. Functional iron deficiency, on the other hand, occurs when iron stores are present but unavailable for utilization, often due to inflammatory-mediated alterations in iron metabolism [2]. In cardiovascular disease, particularly in heart failure, functional iron deficiency is common. Chronic inflammation leads to increased levels of hepcidin, a key regulator of iron homeostasis. Hepcidin reduces intestinal iron absorption and traps iron within macrophages and hepatocytes, limiting its availability for erythropoiesis and cellular metabolism [3]. Because ferritin is an acute-phase reactant, its levels may be normal or elevated in inflammatory states despite underlying iron deficiency. Therefore, the diagnosis in cardiovascular patients relies on a combination of biomarkers rather than a single parameter. Current clinical practice defines iron deficiency in heart failure as: serum ferritin <100 µg/L, or ferritin 100–299 µg/L with transferrin saturation (TSAT) <20%. This definition reflects both absolute and functional iron deficiency and is widely used in clinical trials and guideline recommendations [4]. Transferrin saturation is particularly important, as it reflects the availability of circulating iron for tissue use. Low TSAT indicates impaired iron supply at the cellular level, which is directly relevant to myocardial and skeletal muscle function. Additional markers, such as soluble transferrin receptor and hepcidin levels, have been investigated but are not routinely used in clinical practice due to limited availability and standardization. From a practical perspective, screening for iron deficiency should be considered in patients with heart failure and in other high-risk cardiovascular populations. Early identification allows timely intervention and may improve clinical outcomes.

In summary, iron deficiency in cardiovascular disease is a complex condition influenced by inflammation and altered metabolism. Accurate diagnosis requires the use of combined biomarkers, with ferritin and transferrin saturation remaining the cornerstone of clinical assessment.

3. Pathophysiological Mechanisms of Iron Deficiency in Cardiovascular Disease

Iron plays a fundamental role in cellular metabolism, particularly in oxygen transport, mitochondrial function, and energy production. In cardiovascular disease, iron deficiency disrupts these processes and contributes directly to impaired cardiac and skeletal muscle performance. At the cellular level, iron is essential for mitochondrial oxidative phosphorylation. It is a key component of enzymes involved in the electron transport chain. Iron deficiency leads to reduced adenosine triphosphate (ATP) production, resulting in impaired myocardial contractility and decreased exercise capacity. This mechanism is particularly relevant in heart failure, where energy deficiency is a central feature of disease progression [5]. Iron deficiency also affects skeletal muscle function. Reduced iron availability leads to decreased oxidative capacity and early muscle fatigue. This contributes to exercise intolerance, which is a hallmark symptom in many cardiovascular conditions. Another important mechanism is impaired oxygen transport. Although iron deficiency may occur without anemia, reduced iron availability can still limit hemoglobin function and oxygen delivery at the tissue level. This creates a mismatch between oxygen supply and demand, further exacerbating symptoms such as fatigue and dyspnea. Inflammation plays a central role in the development of iron deficiency in cardiovascular disease. Chronic low-grade inflammation leads to increased hepcidin levels, which reduce intestinal iron absorption and promote sequestration of iron in storage sites. As a result, iron becomes unavailable for metabolic processes despite adequate or even increased total body stores [3].

Iron deficiency also contributes to oxidative stress and endothelial dysfunction. Altered redox balance and reduced activity of iron-dependent enzymes may impair vascular function and promote

atherosclerotic processes. In addition, iron deficiency may influence neurohormonal activation. In heart failure, it has been associated with increased sympathetic activity and activation of the renin–angiotensin–aldosterone system, further contributing to disease progression. Importantly, these mechanisms are not limited to heart failure. Similar metabolic and inflammatory pathways are involved in other cardiovascular conditions, suggesting a broader role of iron deficiency across the cardiovascular spectrum.

In summary, iron deficiency affects cardiovascular function through multiple interconnected mechanisms, including impaired energy production, reduced oxygen utilization, inflammation, and neurohormonal activation. These effects provide a strong biological basis for its clinical impact.

4. Iron Deficiency in Coronary Artery Disease

Iron deficiency is increasingly recognized as a relevant factor in patients with coronary artery disease, although its role is less clearly defined compared to heart failure. Emerging evidence suggests that iron deficiency may influence both disease progression and clinical outcomes in this population.

From a pathophysiological perspective, iron deficiency contributes to impaired myocardial oxygen utilization and reduced cellular energy production. Even in the absence of significant anemia, limited iron availability can affect cardiomyocyte function, particularly under conditions of increased metabolic demand such as ischemia [6]. Inflammation plays a central role in both coronary artery disease and iron metabolism. Chronic vascular inflammation promotes increased hepcidin activity, leading to functional iron deficiency. At the same time, iron deficiency may further amplify inflammatory pathways, creating a bidirectional relationship between iron metabolism and atherosclerosis. Clinical studies have shown that iron deficiency is associated with worse outcomes in patients with coronary artery disease, including higher rates of adverse cardiovascular events and reduced functional capacity. It may also contribute to poorer recovery after acute coronary syndromes.

In the setting of myocardial infarction, iron deficiency may impair myocardial repair processes. Adequate iron availability is necessary for cellular proliferation, mitochondrial function, and tissue regeneration. Deficiency may therefore negatively affect post-infarction remodeling and recovery. Another important aspect is exercise tolerance. Patients with coronary artery disease and iron deficiency often demonstrate reduced exercise capacity, which may not be fully explained by coronary anatomy alone. This highlights the systemic impact of iron deficiency beyond the coronary circulation.

Despite these associations, routine screening for iron deficiency in coronary artery disease is not yet universally recommended. Evidence regarding therapeutic interventions in this population is still limited, and further studies are needed to determine whether correction of iron deficiency improves outcomes.

In summary, iron deficiency may play a significant but underrecognized role in coronary artery disease. Its effects on myocardial metabolism, inflammation, and recovery suggest potential clinical relevance, although its therapeutic implications remain to be fully established.

5. Iron Deficiency in Atrial Fibrillation and Arrhythmias

Iron deficiency is increasingly being explored as a contributing factor in atrial fibrillation and other cardiac arrhythmias. Although the evidence is still emerging, several pathophysiological mechanisms suggest a potential link between altered iron metabolism and electrical instability of the myocardium. At the cellular level, iron is essential for maintaining normal electrophysiological function. It plays a role in mitochondrial energy production and ion channel activity. Reduced availability of iron may impair myocardial energetics, leading to altered cellular electrophysiology and increased susceptibility to arrhythmias [7]. Inflammation represents a key shared pathway between iron deficiency and atrial fibrillation. Chronic low-grade inflammation promotes structural and electrical remodeling of the atria, including fibrosis and conduction abnormalities. Iron deficiency, through its association with inflammatory activation, may contribute to these processes and facilitate the development and maintenance of atrial fibrillation. Another important mechanism

is oxidative stress. Iron-dependent enzymes are involved in maintaining redox balance within cardiomyocytes. Deficiency may disrupt this balance, leading to increased oxidative stress, which is known to promote arrhythmogenesis.

In clinical settings, iron deficiency has been associated with higher prevalence of atrial fibrillation, particularly in patients with heart failure and other comorbidities. It may also influence symptom burden, exercise capacity, and overall functional status in patients with arrhythmias. There is also growing interest in the relationship between iron deficiency and outcomes in patients undergoing catheter ablation. Although data are limited, impaired metabolic and inflammatory status may affect procedural success and recurrence rates. Despite these observations, routine assessment of iron status in patients with atrial fibrillation is not yet standard practice. Evidence regarding the impact of iron repletion on arrhythmia burden or outcomes is currently insufficient, and further studies are required.

In summary, iron deficiency may contribute to the development and progression of atrial fibrillation through mechanisms involving impaired energy metabolism, inflammation, and oxidative stress. While the clinical implications are not yet fully defined, this represents a promising area for future research.

6. Iron Deficiency in Perioperative and Acute Cardiovascular Settings

Iron deficiency is an important but often overlooked factor in perioperative and acute cardiovascular care. In these settings, patients are exposed to increased physiological stress, and adequate iron availability becomes critical for maintaining oxygen delivery, cellular metabolism, and recovery. In cardiac surgery, preoperative iron deficiency has been associated with increased risk of postoperative complications, including prolonged hospital stay, higher transfusion requirements, and delayed recovery. Even in the absence of overt anemia, iron deficiency may impair tissue oxygenation and reduce the capacity to tolerate surgical stress [8]. Blood loss during surgical procedures further exacerbates iron depletion, particularly in patients with already limited iron reserves. This creates a cycle in which iron deficiency contributes to worse outcomes, and surgical stress further aggravates the deficiency. In acute cardiovascular conditions, such as acute coronary syndromes and acute heart failure, iron deficiency may negatively influence clinical stability and recovery. Reduced availability of iron can impair myocardial energetics at a time when metabolic demand is increased, potentially worsening ischemic injury and delaying functional recovery. Iron deficiency may also affect hemodynamic stability. Impaired oxygen delivery and reduced cellular energy production can contribute to fatigue, hypotension, and delayed mobilization in the acute phase of illness. From a clinical perspective, there is increasing interest in preoperative optimization of iron status. In non-cardiac surgery, correction of iron deficiency has been shown to reduce transfusion rates and improve outcomes. Similar strategies are being explored in cardiac patients, although evidence remains limited. In acute settings, routine screening for iron deficiency is not yet standard practice. However, identifying patients with significant deficiency may provide an opportunity for targeted intervention, particularly in those with high-risk profiles. Another important consideration is the use of intravenous iron therapy. Oral iron is often ineffective in acute or inflammatory states due to impaired absorption, while intravenous formulations allow rapid repletion of iron stores. Their role in perioperative and acute cardiovascular care is an area of ongoing research.

In summary, iron deficiency may influence outcomes in perioperative and acute cardiovascular settings by impairing oxygen delivery, metabolic function, and recovery. Recognition of this condition may improve risk stratification and support more effective patient management.

7. Therapeutic Strategies: Iron Replacement Beyond Heart Failure

Correction of iron deficiency has become an established component of heart failure management, but its role in other cardiovascular conditions is still evolving. Therapeutic strategies focus on restoring iron availability to improve cellular metabolism, functional capacity, and clinical outcomes.

Oral iron supplementation is widely available and commonly used in general practice. However, in cardiovascular patients—particularly those with chronic inflammation—its effectiveness is limited. Elevated levels of hepcidin reduce intestinal iron absorption, leading to poor bioavailability. In addition, gastrointestinal side effects often reduce adherence [3]. Intravenous iron therapy provides a more effective alternative by bypassing intestinal absorption and allowing rapid replenishment of iron stores. Ferric carboxymaltose is the most extensively studied formulation in cardiovascular disease. Clinical trials in heart failure have demonstrated improvements in exercise capacity, symptoms, and quality of life, as well as reductions in hospitalizations [5]. Although most of the evidence comes from heart failure populations, the underlying mechanisms suggest potential benefits in other cardiovascular conditions. Improved mitochondrial function, enhanced oxygen utilization, and reduced fatigue may be relevant across a broader spectrum of diseases. In patients with coronary artery disease, the role of iron therapy is less well established. While observational data suggest an association between iron deficiency and worse outcomes, randomized trials evaluating the effect of iron repletion are limited. Therefore, routine use of intravenous iron in this population is not currently recommended.

Similarly, in atrial fibrillation and other arrhythmias, there is insufficient evidence to support targeted iron therapy. However, correction of significant deficiency may still be reasonable in symptomatic patients, particularly when associated with reduced functional capacity. In perioperative settings, intravenous iron has shown benefits in reducing transfusion requirements and improving recovery in selected surgical populations. Its role in cardiac patients is an area of ongoing investigation. Safety considerations are also important. Modern intravenous iron formulations have a favorable safety profile, with low rates of serious adverse reactions. Nonetheless, appropriate patient selection and monitoring remain essential.

In summary, intravenous iron therapy is an effective strategy for correcting iron deficiency in heart failure and may have broader applications in cardiovascular disease. However, its use outside heart failure should be individualized and guided by emerging evidence.

8. Clinical Implications and Screening Strategies

Recognition of iron deficiency in cardiovascular patients has important clinical implications, particularly in improving diagnosis, risk stratification, and patient management beyond heart failure.

One of the key challenges is underdiagnosis. Iron deficiency is frequently overlooked because symptoms such as fatigue, reduced exercise tolerance, and dyspnea are often attributed solely to underlying cardiovascular disease. As a result, a potentially modifiable contributor to clinical status remains untreated. Routine screening for iron deficiency is well established in heart failure but is less consistently applied in other cardiovascular conditions. Expanding screening strategies to include patients with coronary artery disease, atrial fibrillation, and high-risk perioperative profiles may allow earlier identification of clinically relevant deficiency. From a practical perspective, assessment should include both serum ferritin and transferrin saturation. Reliance on a single parameter may lead to misclassification, particularly in the presence of inflammation. Combined interpretation provides a more accurate reflection of iron status and availability. Iron deficiency also has prognostic implications. It has been associated with reduced functional capacity, higher hospitalization rates, and worse clinical outcomes in several cardiovascular populations. Identifying affected patients may therefore improve risk stratification and guide closer follow-up. In addition, recognition of iron deficiency can influence therapeutic decisions. In selected patients, correction of deficiency may improve symptoms and functional status, even when the primary cardiovascular condition is optimally treated. This highlights the importance of a comprehensive approach that addresses both cardiac and systemic factors. Another important aspect is integration into clinical pathways. Incorporating iron status assessment into routine evaluation—particularly in outpatient clinics and during hospitalization—may improve detection rates and facilitate timely intervention. Patient education is also relevant. Informing patients about the role of iron deficiency and its impact on symptoms may improve adherence to diagnostic and therapeutic strategies. Despite these

considerations, widespread screening in all cardiovascular patients is not yet supported by strong evidence. A targeted approach focusing on high-risk populations is currently more appropriate.

In summary, iron deficiency represents a clinically relevant and potentially modifiable factor in cardiovascular disease. Improved recognition and targeted screening may enhance patient management and outcomes.

9. Conclusion

Iron deficiency is increasingly recognized as a clinically relevant comorbidity across the cardiovascular spectrum and not only in heart failure. Its effects extend beyond anemia and include impaired myocardial energetics, reduced skeletal muscle performance, decreased exercise capacity, and worse clinical outcomes. Current guideline-based diagnostic thresholds in heart failure rely on ferritin and transferrin saturation, reflecting the need to identify both absolute and functional iron deficiency.

The strongest therapeutic evidence remains in heart failure, where intravenous ferric carboxymaltose has shown benefits in symptoms, functional capacity, and reduction in heart failure events. Outside heart failure, the biological rationale is strong, but the clinical evidence is still limited and does not yet support broad routine treatment across all cardiovascular conditions.

From a practical perspective, iron deficiency should be viewed as a potentially modifiable contributor to cardiovascular burden. Its recognition may improve risk stratification, clarify persistent symptoms, and support a more comprehensive management strategy. Future studies should determine whether systematic screening and targeted iron repletion can improve outcomes in coronary artery disease, atrial fibrillation, and acute or perioperative cardiovascular settings.

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