THE ROLE OF HEPCIDIN IN PATIENTS WITH HEART FAILURE AND RHEUMATOID ARTHRITIS

Roziqov S.G.[1], Xasanov F.Sh. [1]

1. Samarkand State Medical University, Samarkand, Uzbekistan

ABSTRACT

Hepcidin is the central peptide hormone regulating systemic iron homeostasis and has increasing clinical relevance in chronic inflammatory diseases, particularly heart failure and rheumatoid arthritis. In both conditions, inflammation, impaired iron trafficking, reduced iron bioavailability and anemia contribute to fatigue, exercise intolerance, reduced quality of life and worse prognosis. Hepcidin is mainly produced by hepatocytes and is upregulated by interleukin-6, inflammation and iron loading, while it is suppressed by iron deficiency, hypoxia and increased erythropoietic demand. By binding to ferroportin, hepcidin prevents intestinal iron absorption and macrophage iron export, producing functional iron deficiency despite normal or elevated ferritin. In heart failure, hepcidin biology is complex because absolute iron deficiency, chronic inflammation, renal dysfunction and myocardial iron handling may coexist. In rheumatoid arthritis, IL-6-driven hepcidin elevation is a major mechanism of anemia of chronic disease and correlates with inflammatory activity in several studies. Therapeutically, intravenous iron improves outcomes in selected heart failure patients, whereas IL-6 inhibition in rheumatoid arthritis can reduce hepcidin and improve hemoglobin. This review summarizes hepcidin biology, its diagnostic significance, disease-specific mechanisms and therapeutic implications in heart failure and rheumatoid arthritis.

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Introduction

Hepcidin has transformed the modern understanding of anemia in chronic inflammatory diseases. Before the discovery of hepcidin, anemia in chronic disease was explained mainly by "iron sequestration," impaired erythropoiesis and cytokine-mediated bone marrow suppression. Current evidence shows that hepcidin is the principal molecular link between inflammation and iron restriction [1–5]. This is particularly important in heart failure (HF) and rheumatoid arthritis (RA), where fatigue and reduced functional capacity are often attributed to the primary disease, although iron dysregulation may be a major independent contributor [6–11,19–25].

HF and RA appear clinically different, but they share several pathophysiological features: chronic systemic inflammation, elevated interleukin-6 (IL-6), altered iron metabolism, anemia, reduced physical performance and high comorbidity burden [4,6,19,27,31]. In HF, iron deficiency may occur with or without anemia and is associated with reduced exercise capacity, worse quality of life, higher hospitalization risk and adverse prognosis [6–9,17]. In RA, anemia is one of the most frequent extra-articular manifestations, and hepcidin is strongly implicated in the anemia of chronic inflammation [19–25]. Key RA hepcidin studies and HF iron-deficiency reviews are indexed in PubMed/PMC or publisher databases, including RA disease-activity studies and HF iron-deficiency mechanistic reviews.

Biological basis of hepcidin

Hepcidin is a small peptide hormone encoded by the HAMP gene and produced mainly by the liver. Its primary target is ferroportin, the only known cellular iron exporter. Ferroportin is expressed on enterocytes, macrophages, hepatocytes and placental cells. When hepcidin binds ferroportin, ferroportin is internalized and degraded. As a result, dietary iron absorption decreases and macrophage iron release is blocked [1–5].

This mechanism explains the biochemical pattern of functional iron deficiency: ferritin may be normal or high because iron is stored in macrophages and hepatocytes, while transferrin saturation is low because circulating iron is unavailable for erythropoiesis and tissue metabolism [2–5]. In chronic inflammation, IL-6 activates the JAK/STAT3 pathway and increases hepatic hepcidin transcription [1,27,28]. Therefore, hepcidin is not merely a marker of iron metabolism; it is a mediator of inflammation-induced iron restriction.

- Hepcidin is regulated by four major biological signals:
- Inflammation: IL-6, IL-1β and other cytokines increase hepcidin synthesis [1,27,28].
- Iron loading: high body iron stores stimulate hepcidin to prevent further iron absorption [2,3,5].
- Iron deficiency and hypoxia: these suppress hepcidin to increase iron availability [2,3,33].
- Erythropoietic activity: increased erythropoiesis suppresses hepcidin through erythroferrone and related pathways [5].

This balance is clinically important because hepcidin can be high, normal or low depending on whether inflammation or absolute iron depletion is dominant. Thus, interpretation of hepcidin in HF or RA requires simultaneous assessment of ferritin, transferrin saturation, CRP, renal function and hemoglobin [4–6,23–25].

Hepcidin, iron deficiency and anemia: core mechanisms

Anemia in chronic disease is usually normocytic or mildly microcytic and is characterized by low serum iron, low transferrin saturation, normal or increased ferritin and reduced iron availability for erythropoiesis [4,32]. Hepcidin contributes to this syndrome through three mechanisms.

First, it reduces intestinal iron absorption by degrading ferroportin on enterocytes [1–3]. Second, it traps iron inside macrophages, limiting iron recycling from senescent erythrocytes [2–5]. Third, it indirectly reduces erythropoietic efficiency because the bone marrow receives insufficient iron despite adequate total body iron stores [4,32].

In clinical practice, this creates a diagnostic challenge. Ferritin alone is unreliable during inflammation, because ferritin is also an acute-phase reactant [4,6,32]. A patient with RA or HF may have "normal" ferritin but insufficient bioavailable iron. Therefore, combined interpretation of transferrin saturation (TSAT), ferritin, CRP and hemoglobin is more clinically meaningful than any single marker [6,16,23–25].

Hepcidin in heart failure

Iron deficiency is common in HF and may occur independently of anemia [6–9]. It is clinically important because iron is required not only for hemoglobin synthesis but also for mitochondrial oxidative phosphorylation, skeletal muscle function and myocardial energetics [6,8,9]. Patients with HF and iron deficiency often have lower peak oxygen uptake, worse New York Heart Association functional class and poorer quality of life [8,9].

The standard HF definition of iron deficiency has usually been: serum ferritin <100 μg/L, or ferritin 100–299 μg/L with TSAT <20% [10–16]. This definition is practical but imperfect because ferritin is influenced by inflammation. Hepcidin may theoretically improve classification by distinguishing absolute iron deficiency from functional iron deficiency, but standardized clinical cut-offs are not yet established [6,16]. Recent reviews emphasize that hepcidin remains mainly a research biomarker in HF because assays are not fully standardized and clinical thresholds remain uncertain.

In RA, inflammation often drives hepcidin upward. In HF, the pattern is more heterogeneous. Some HF patients have increased inflammatory signaling that can raise hepcidin, especially in advanced disease, renal dysfunction or high CRP states [6,12,13]. However, many HF patients also have absolute iron deficiency due to poor dietary intake, gastrointestinal blood loss, anticoagulant use, intestinal edema, reduced absorption or repeated hospitalization. In absolute iron deficiency, hepcidin may be suppressed [6,11,15].

Therefore, HF can present with at least three iron-metabolic phenotypes:

Phenotype	Typical pattern	Hepcidin tendency	Clinical meaning
Absolute iron deficiency	Low ferritin, low TSAT	Low	Depleted iron stores
Functional iron deficiency	Normal/high ferritin, low TSAT, high CRP	Normal/high	Iron trapped in stores
Mixed deficiency	Borderline ferritin, low TSAT, inflammation	Variable	Common in real-world HF

This explains why hepcidin alone should not be used as a replacement for standard iron indices. Instead, it may become useful as an additional biomarker for iron phenotype classification, prediction of oral iron response and selection of iron therapy [6,15,16].

Hepcidin and myocardial iron metabolism

The role of hepcidin in HF is not limited to systemic iron metabolism. Experimental and translational data suggest that local cardiac iron handling may influence myocardial function. Cardiomyocytes require iron for mitochondrial respiration, and myocardial iron depletion may impair energy production, contractility and cellular survival [6,12,13]. Some studies suggest that hepcidin-ferroportin signaling may also operate within the heart, although its clinical interpretation remains less developed than systemic hepcidin biology [12,13].

This is important because HF is fundamentally an energetic disorder. Reduced iron availability may worsen myocardial and skeletal muscle bioenergetics even before severe anemia develops [6,8,9]. Therefore, iron deficiency in HF should be considered a tissue-metabolic problem, not merely a hematological abnormality.

Therapeutic implications in HF

Several randomized trials have shown that intravenous iron, especially ferric carboxymaltose, improves symptoms, exercise capacity and quality of life in selected patients with HF and iron deficiency [10–12]. The FAIR-HF and CONFIRM-HF trials supported symptomatic and functional benefits [10,11]. AFFIRM-AHF suggested reduction in HF hospitalizations after acute HF stabilization, although effects on mortality were not definitive [12]. IRONMAN and HEART-FID provided more nuanced results, indicating that benefits may depend on population selection, endpoint choice, formulation, follow-up and baseline iron phenotype [13,14].

Oral iron has generally been less effective in HF. The IRONOUT-HF trial showed that high-dose oral iron polysaccharide did not significantly improve exercise capacity in patients with HFrEF and iron deficiency [15]. A plausible biological explanation is that inflammation and hepcidin-mediated ferroportin blockade reduce intestinal iron absorption [1–3,15]. Thus, in HF patients with inflammation-

driven functional iron deficiency, intravenous iron bypasses the hepcidin-restricted intestinal absorption pathway.

Hepcidin in rheumatoid arthritis

RA is a chronic autoimmune inflammatory disease characterized by synovitis, systemic inflammation and extra-articular manifestations [29–31]. Anemia in RA may result from anemia of chronic disease, absolute iron deficiency, drug-related gastrointestinal bleeding, renal disease or mixed mechanisms [19,23–25]. Hepcidin is particularly relevant because RA is strongly associated with IL-6 activation, and IL-6 is one of the strongest inflammatory inducers of hepcidin [1,19,20,27,28].

In RA, elevated hepcidin reduces serum iron and transferrin saturation while maintaining or increasing ferritin. This creates functional iron restriction and contributes to fatigue, reduced physical performance and impaired quality of life [19–25]. Several RA studies have shown associations between hepcidin or pro-hepcidin and disease activity, CRP, ESR, DAS28 and anemia parameters [22–25]. RA-specific studies report that circulating hepcidin is related to inflammatory activity and anemia of chronic disease, although results vary depending on whether patients have pure inflammatory anemia or mixed iron deficiency.

Kim et al. reported that serum pro-hepcidin was higher in active RA than in inactive or moderate disease [22]. Sahebari et al. found that serum hepcidin was associated with RA disease activity [23]. Khalaf et al. investigated hepcidin in RA anemia and highlighted its relationship with iron status, CRP, ESR and DAS28 [24]. Nita et al. further emphasized the role of hepcidin in anemia of chronic disease in RA and its association with inflammatory and erythropoietic markers [25].

The clinical interpretation is clear: in RA, high hepcidin usually reflects inflammation-mediated iron restriction. However, low hepcidin does not exclude RA activity; it may indicate concomitant absolute iron deficiency, especially in patients with gastrointestinal blood loss, poor nutrition or long-term non-steroidal anti-inflammatory drug use [21,24,25].

The strongest therapeutic evidence connecting RA inflammation, hepcidin and anemia comes from studies of IL-6 receptor inhibition. Tocilizumab reduces IL-6 signaling and can decrease hepcidin, improve iron availability and increase hemoglobin [20,21]. Song et al. reported that tocilizumab improved RA anemia and normalized iron metabolism more effectively than TNF-α inhibitors, consistent with stronger inhibition of the IL-6–hepcidin axis [20]. Isaacs et al. also showed that tocilizumab-induced changes in hematologic markers are linked to acute-phase response modulation [21].

This does not mean that hepcidin should replace standard RA activity markers. Rather, hepcidin may serve as a mechanistic biomarker connecting inflammation, iron restriction and anemia. It may be especially useful in RA patients with persistent fatigue and anemia despite conventional treatment.

Comparison between HF and RA

HF and RA both involve hepcidin, but the dominant mechanisms differ.

Feature	Heart failure	Rheumatoid arthritis
Main driver	Iron deficiency, inflammation, renal dysfunction, congestion	IL-6-driven systemic inflammation
Hepcidin pattern	Variable: low, normal or high	Often elevated in active inflammatory disease
Main iron phenotype	Absolute, functional or mixed deficiency	Functional deficiency; mixed deficiency also common
Main clinical consequence	Reduced exercise capacity, poor QoL, HF hospitalization	Anemia, fatigue, disease-activity-related iron restriction
Therapeutic implication	IV iron may improve symptoms and reduce hospitalization risk in selected patients	IL-6 inhibition may reduce hepcidin and improve anemia
Diagnostic limitation	Ferritin distorted by inflammation; hepcidin assays not standardized	Hepcidin affected by both inflammation and true iron deficiency

The most important distinction is that HF iron deficiency is not always hepcidin-high, whereas RA inflammatory anemia is more classically hepcidin-driven. In HF, low hepcidin may reflect absolute iron depletion and predict better iron absorption, although oral iron still performs poorly in many patients [15]. In RA, high hepcidin often indicates active inflammation and functional iron blockade [19–25].

Diagnostic implications

For HF patients: hemoglobin, ferritin, TSAT, CRP, renal function, natriuretic peptides and clinical congestion status [6,16]. Hepcidin may be useful in research settings to distinguish absolute from functional iron deficiency, but routine use is limited by assay variability and lack of universal cut-offs [6,16].

For RA patients: hemoglobin, MCV, ferritin, TSAT, serum iron, CRP, ESR, DAS28, renal function and medication history [23–25,29]. Hepcidin may help differentiate anemia of chronic disease from absolute iron deficiency when interpreted with CRP and ferritin.

A simplified interpretation model:

Ferritin	TSAT	CRP	Hepcidin	Likely interpretation
Low	Low	Any	Low	Absolute iron deficiency
Normal/high	Low	High	High	Functional iron deficiency / inflammatory anemia
Normal/high	Low	High	Low/normal	Mixed state or inflammation plus depleted stores
High	Normal	High	High	Inflammation with preserved circulating iron

Therapeutic implications

In HF, the clinically proven intervention is not direct hepcidin inhibition but **intravenous iron replacement** in patients meeting guideline-based iron deficiency criteria [10–16]. IV iron bypasses the hepcidin-regulated intestinal absorption barrier and can improve functional status. However, trial results are heterogeneous, and mortality benefit remains uncertain [12–14].

Future HF treatment strategies may include better phenotyping of patients by TSAT, ferritin, CRP and possibly hepcidin. Patients with high hepcidin and functional iron restriction may respond differently from those with low hepcidin and absolute deficiency. This remains an important research area.

In RA, treating the inflammatory driver is central. Effective suppression of IL-6 signaling can reduce hepcidin and improve anemia [20,21]. TNF inhibitors may also improve inflammation-related anemia, but the hepcidin effect appears more direct with IL-6 blockade [20]. Iron therapy should be individualized: oral or IV iron may be appropriate in absolute deficiency, but giving iron without controlling inflammation may be less effective when hepcidin remains high [19,24,25].

Research gaps

Despite strong biological plausibility, several gaps remain:

1. **Assay standardization:** hepcidin measurement lacks universal standardization across laboratories [6,16].
2. **Clinical thresholds:** validated cut-offs for HF and RA are not established.
3. **Longitudinal data:** more studies are needed to determine whether hepcidin predicts hospitalization, mortality, treatment response or RA remission.
4. **Mixed anemia phenotypes:** many patients have both absolute iron deficiency and inflammatory iron restriction.
5. **Integrated treatment algorithms:** future studies should test whether hepcidin-guided treatment improves outcomes compared with ferritin/TSAT-guided treatment alone.

Conclusion

Hepcidin is a key mechanistic bridge between inflammation, iron metabolism and anemia in both heart failure and rheumatoid arthritis. In HF, hepcidin contributes to functional iron deficiency, but its level may vary because absolute iron deficiency and inflammation often coexist. In RA, IL-6-driven hepcidin elevation is a central mechanism of anemia of chronic disease and is closely connected with inflammatory activity. Clinically, hepcidin helps explain why ferritin may be misleading, why oral iron often fails in inflammatory states and why IV iron or IL-6 inhibition may improve patient outcomes. At present, hepcidin is more useful as a mechanistic and research biomarker than as a routine clinical test. Future hepcidin-guided strategies may improve personalized treatment of anemia and iron deficiency in HF and RA.

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