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Iron Dysregulation in Sickle Cell Disease: Trend and Clinical Implications

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Abstract

Iron imbalance in sickle cell disease (SCD) is a complex puzzle that leads to persistent hemolysis, recurrent transfusions, and dysregulated iron metabolism. This brief review examines the key trends in iron homeostasis, overload, and deficiency in SCD, exploring the underlying mechanisms, clinical implications, and therapeutic approaches. Iron overload frequently arises from transfusion therapy, although iron shortage may also result from heightened erythropoietic demand and inflammation. We highlight the functions of serum ferritin, transferrin saturation (TSAT), hepcidin, and new biomarkers, as well as therapeutic strategies encompassing chelation and innovative treatments. This review synthesizes current findings, identifies knowledge gaps, and suggests future research directions to enhance iron-related outcomes in sickle cell disease (SCD).

Keywords: Sickle cell disease, iron overload, iron deficiency, transfusion, chelation therapy, hemolysis, Iron, Ferritin, TSAT.

1. Introduction

Sickle cell disease (SCD), a group of hereditary conditions resulting from abnormalities in both β-globin component alleles, is estimated to affect around 5.7 million individuals worldwide [1]. All variants of SCD are defined by the presence of at least one β^S allele in the hemoglobin subunit β-gene. β^S homozygosity is diagnostic for sickle cell anemia (SCA), the predominant variant of SCD, while a β^S/β^C genotype leads to hemoglobin SC disease (HbSC). HbSβ-thalassemia arises from the combination of a β^S allele with either a β^0 (null β-gene) or a β+ (hypomorphic β-gene) thalassemia mutation. Both HbSC and HbSβ^+ typically result in a clinical presentation that is less severe than SCA, especially in young individuals [2]. Due to the partial resistance to malaria conferred by the sickle cell trait (i.e., AS heterozygotes), the prevalence of SCD has traditionally been most notable in areas where malaria is endemic [3,4]. Currently, around 300,000 newborns are born each year globally with SCD [5].

Despite the development and approval of novel pharmaceutical treatments, the burden of SCD remains significant, especially in areas with restricted access to treatment. This factor has a significant impact on the lives of SCD patients. In sub-Saharan Africa, about 50% of babies with sickle cell disease do not live beyond five years [6]. In areas with superior access to high-quality healthcare, including drugs and blood transfusions, such as the United States, life expectancy for those with SCD remains 20–30 years less than that of individuals without the condition [7]. Understanding the clinical signs of SCA, which arise from elevated blood viscosity and vascular blockage caused by malformed sickled red blood cells RBCs, is crucial. The decreased flexibility of red blood

cells leads to stroke, splenic sequestration crisis, aplastic crisis, infections, and skeletal injury. Patients with sickle cell anemia exhibit elevated body iron concentrations compared to individuals without the condition, highlighting the necessity of your role in managing this disease [8].

Iron excess induces toxicity and cellular apoptosis by generating free radicals and lipid peroxidation. Conversely, overt iron deficiency, characterized by diminished serum ferritin levels, can manifest in SCA despite significant hemosiderosis [9]. The surplus iron deposits are inaccessible for erythropoiesis and may not be indicated in serum ferritin levels. Iron deficiency anemia can coexist in patients with sickle cell anemia, as they remain susceptible to environmental conditions that induce iron deficiency anemia. In the tropics, factors such as inadequate nutrition, parasite infestations, and diverse bacterial diseases can disrupt iron metabolism [10]. Furthermore, significant iron loss in the urine, inadequate iron absorption and metabolism resulting from numerous mucosal/submucosal infarctions, and progressive organ damage render patients very vulnerable to iron deficiency anemia [9]. An iron shortage or overload exacerbates SCA and will likely worsen the clinical situation [11]. Consequently, iron hemostasis necessitates stringent management to prevent problems [12].

Patients with SCD experience persistent hemolytic anemia, leading to increased iron turnover. The delicate balance of iron homeostasis is disrupted by transfusion-related iron overload in frequently transfused patients, potentially leading to serious complications. The role of inflammation and hepcidin deregulation in causing functional iron deficit is a key aspect of the complex iron metabolism in SCD patients. Mixed iron disorders (the simultaneous presence of hepatic iron overload and erythropoietic protoporphyria) [13, 14] [**Figure 1**]. Regular monitoring of iron indices is crucial in caring for SCD patients, as it helps prevent complications such as iron overload, cardiomyopathy, or inadequate erythropoiesis.

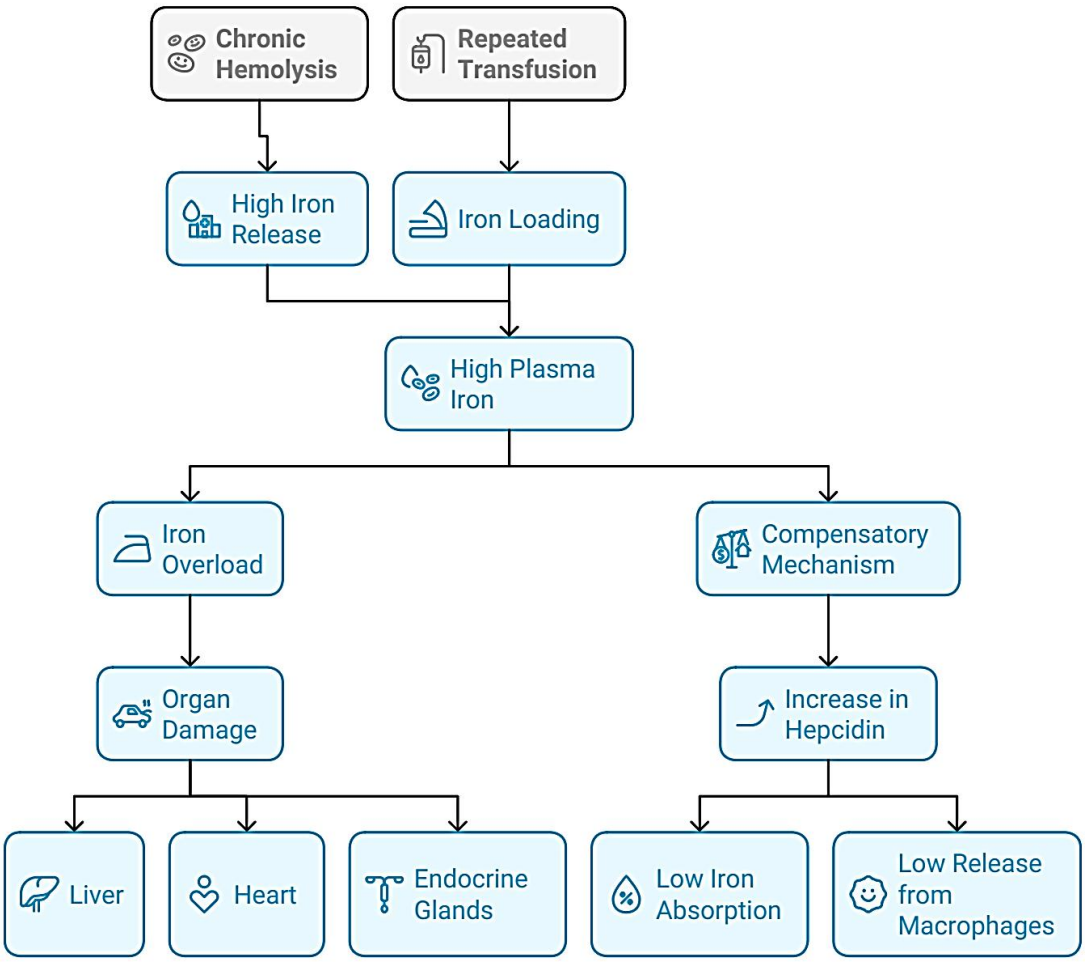

Figure 1: Illustration of Iron dysregulation in SCD

2. Iron metabolism in SCD

Iron status is typically evaluated in healthy populations using comprehensive methods. These include a full blood count with RBC indices and morphology, serum ferritin concentrations, and transferrin saturation (TSAT) values. When necessary, more sophisticated laboratory markers (e.g., erythrocyte zinc protoporphyrin, hepcidin, soluble transferrin receptors, reticulocyte hemoglobin content, non-transferrin-bound iron [NTBI]) as well as magnetic resonance imaging and bone marrow biopsies, may be conducted to ensure a thorough and accurate evaluation [15]. SCD is often defined by normal iron distribution, adequate iron storage, or relative iron insufficiency [16]. Except for potential iron accumulation in the kidneys associated with prolonged intravascular hemolysis, non-transfused patients with sickle cell disease do not demonstrate clinical, biochemical, or radiologic signs of excessive iron levels [17].

2.1 Source of Iron in SCD

Hemolysis: The intravascular and extravascular destruction of sickle red blood cells releases iron, which is predominantly recycled by the body's iron metabolism system.

Transfusions: Each unit of packed red blood cells contains approximately 200–250 mg of iron, which can lead to a significant buildup in patients receiving continuous transfusions, underscoring the gravity of this issue in SCD management.

Nutritional absorption: Inflamed SCD patients may experience decreased absorption due to the role of hepcidin, a key regulator of iron metabolism [14].

2.2 Hepcidin deregulation

Hepcidin, the principal regulator of iron, is often downregulated in anemia to facilitate increased iron absorption. However, patients with SCD frequently exhibit increased hepcidin levels, which are attributable to chronic inflammation induced by IL-6 stimulation. IL-6, a pro-inflammatory cytokine, is known to stimulate hepcidin production in the liver, resulting in increased blood levels of hepcidin. This chronic inflammation, often observed in SCD patients, leads to increased hepcidin levels, resulting in compromised iron mobilization in the presence of systemic iron overload [18,19].

3. Key Iron Indices in SCD

3.1. Serum Ferritin

- A standard indicator of iron reserves, although influenced by inflammatory processes. The interpretation of serum ferritin levels as an indicator of iron status in SCD is complicated by ferritin's function as an acute-phase reactant and the high incidence of vascular and systemic inflammation caused by repeated vaso-occlusion [1]. Nonetheless, a low ferritin level indicates diminished body iron, even in SCD. Anticipating changes in hepcidin levels due to SCD is crucial for understanding iron homeostasis. Ineffective erythropoiesis and chronic hemolytic anemia are expected to lower hepcidin levels, while inflammation and elevated blood iron concentrations likely stimulate hepcidin expression [20]. Variations in inflammation in SCD may elucidate the contradictory evidence about hepcidin and ferritin levels in SCD. Compared to healthy adult controls, ferritin levels were often elevated in SCA, attributable to a combination of inflammation and transfusion therapy [10].

- **Summary of Interpretation:**

Levels exceeding 1,000 ng/mL indicate iron overload in individuals who have received transfusions [**Table 1**]. Normal or low ferritin levels accompanied by anemia may suggest functional iron shortage.

- **Limitations:** Acute-phase reactant (artificially elevated in VOC/infection) vaso-occlusive crisis.

Table 1: Interpretation of Iron Biomarker in SCD

Biomarker	Normal Value	SCD Interpretation	Limitations
Serum Ferritin	20 – 300 ng/ml	1000 ng/ml = iron overload [20]	Falsely elevated in inflammation
TSAT	20 – 45%	45% = Overload; <20% = deficiency [21]	Affected by the recent transfusion

sTfR	0.76 – 1.76 mg/L	High in iron deficiency [22]	Not routine in clinical practice
Hepcidin	5 – 30 ng/ml	High in inflammation [19]	Limited availability
LIC (MRI-R2)	< 3.0 mg/g	7 mg/g = severe overload [23]	Costly, requires expertise

TSAT; transferrin saturation, sTfR; soluble transferrin receptor, LIC (MCRI); liver iron concentration (magnetic resonance imaging)

3.2. Transferrin Saturation (TSAT)

- TSAT = (Serum Iron / TIBC) × 100

- High TSAT (>45%): Indicates iron overload, a common condition in patients with SCD who have received transfusions.

- Low TSAT (<20%): Suggests iron deficiency or sequestration [21].

3.3. Liver Iron Concentration (LIC) – Gold Standard

- MRI (T2/R2) quantifies hepatic iron (non-invasive).

- A LIC greater than 3 mg/g dry weight indicates iron overload [23].

3.4. Soluble Transferrin Receptor (sTfR)

- Elevated in iron deficiency (unaffected by inflammation).

- Useful for detecting functional iron deficiency in SCD [22].

3.5. Hepcidin Levels

Omena et al. detected that the highest hepcidin concentrations were observed in patients with SCD who exhibited potential iron overload, as indicated by serum ferritin levels of 1000 ng/mL or higher [20].

- High hepcidin: Limits iron absorption and mobilization, worsening anemia.

- Potential therapeutic target (e.g., hepcidin antagonists in clinical trials) [19].

4. Clinical Scenarios & Challenges [Table 2]

4.1. Iron Overload in Transfused Sickle Cell Disease

At baseline, individuals with SCD do not seem to be at risk for iron overload. Repeated blood transfusions unequivocally lead to iron overload, albeit to a lesser extent than that seen in individuals with other chronic hemolytic conditions, such as β-thalassemia. In patients with SCD undergoing transfusion therapy, iron overload is less likely to affect the endocrine glands and heart, mostly accumulating in the liver and spleen [24]. Although patients with SCD undergoing chronic transfusions exhibit a reduced overall risk of iron overload and its associated consequences, it is imperative to evaluate liver iron levels every 1 to 2 years. Regrettably, figures indicate that present screening rates are inadequate, with only 32% of children and 41% of adults undergoing suitable evaluations [25]. This situation could lead to serious health consequences, underscoring the need for improved screening practices.

- **Principal cause:** Chronic transfusions (e.g., for stroke prophylaxis).

-**Surveillance:** Annual assessment of ferritin, transferrin saturation (TSAT), and magnetic resonance imaging of liver iron concentration (MRI-LIC).

- Management:

- Chelation therapy (deferasirox, deferoxamine).

- Phlebotomy (contingent upon hemoglobin levels) [23].

4.2. Functional Iron Deficiency with SCD

Functional iron deficiency (FID) is a complex condition. It involves a paradox where there are sufficient or excessive iron reserves, but iron is inaccessible for erythropoiesis due to chronic inflammation and hepcidin-mediated iron sequestration. FID in SCD is influenced by inflammation and hepcidin-mediated iron blockade. The management of this condition emphasizes the need to mitigate inflammation rather than administer iron supplementation [26]. Your actions in managing inflammation are crucial, as they directly impact the well-being of patients with sickle cell disease (SCD).

- Occurs regardless of normal or elevated ferritin levels, attributable to hepcidin inhibition.
- Diagnosis: Elevated sTfR, decreased TSAT, normal to elevated ferritin levels.
- Treatment: Erythropoietin (seldom utilized in SCD due to the risk of stroke).
- Experimental: Hepcidin antagonists.

4.3. Combined Iron Disorders

In SCD, patients can develop a mixed iron disorder, where FID coexists with systemic iron overload. This paradoxical state arises due to the dual pathology of ineffective erythropoiesis + chronic inflammation (causing FID) and frequent transfusion chronic hemolysis (leading to iron overload) [14].

– Simultaneous iron overload (hepatic) and deficiency (erythropoiesis).

– Demands personalized management (e.g., chelation therapy with tailored iron supplementation).

Table 2: Clinical Scenarios and Diagnostic Approach

Condition	Key Biomarkers	Management
Transfusion overload	Ferritin > 1000, TSAT > 45%, LIC↑	Chelation (Deferasirox) [20]
Functional deficiency	High sTfR, normal ferritin, TSAT < 20%	Hepcidin modulators [19]
Combined disorder	High LIC + Low TSAT	Individualized therapy [14]

TSAT; transferrin saturation, sTfR; soluble transferrin receptor, LIC: liver iron concentration

5. Novel Biomarkers [Table 3]

SCD poses a distinct challenge to iron homeostasis due to persistent hemolysis, inflammation, and transfusion-related iron overload. However, discovering novel biomarkers and mechanisms provides fresh perspectives on iron dysregulation and prospective treatment strategies, instilling a sense of hope and optimism in the audience.

- **Erythroferrone** (ERFE): A hormone secreted by erythroblasts in response to erythropoietin (EPO), which suppresses hepcidin to enhance iron metabolization for erythropoiesis. Relevance in SCD chronic hemolysis and EPO stimulation should increase ERFE, decrease hepcidin, and increase iron release. However, in SCD, inflammation (IL-6) overrides ERFE, resulting in the maintenance of high hepcidin levels and iron restriction. Clinical utility may aid in evaluating inefficient erythropoiesis and identifying therapeutic targets, such as ERFE mimetics or hepcidin inhibitors, which are currently in development [27].

- **Reticulocyte hemoglobin content** (Ret-He): Measures the iron availability for new red blood cell production, reflecting recent iron incorporation. Advantages over ferritin/TSAT: not confounded by inflammation, an early marker of functional iron deficiency (identifies early iron-deficient erythropoiesis) (low Ret-He = insufficient iron for erythropoiesis). Predicts response to erythropoiesis-stimulating agents (ESAs) [28].

- **Non-transferrin-bound iron** (NTBI) and **Labile plasma iron** (LPI) indicate the potential for hazardous iron accumulation. NTBI: Toxic, unbound iron in plasma occurs when transferrin is saturated with iron. LPI: Redox-active NTBI fraction, which causes oxidative damage. In SCD implication: transfused patients often have ↑ NTBI/LPI → endothelial damage, vaso-occlusion risk. Chelation therapy reduces NTBI/PLI (monitored via LPI assays) [29].

Growth differentiation factor 15 (GDF15): Similar to ERFE, stressed erythroblasts secrete it and suppress hepcidin. In the SCD context, elevated levels cannot overcome the inflammatory drive of hepcidin. GDF15 may help stratify patients for hepcidin-modulating therapies [30].

Table 3: Novel iron markers

Biomarker	Role in SCD	Clinical Utility
Erythroferrone	Low hepcidin during hemopoiesis	Predict iron demand [27]
NTBI	Toxic-free iron	Assess oxidative risk [29]
Ret-He	Reticulocyte hemoglobin content	Early iron restriction [28]

NTBI; non-transferrin-bound iron

6. Perspective Therapeutic pathways in SCD Iron dysregulation

Novel therapeutics address the intricate relationship between iron restriction and excess in sickle cell disease (SCD). Modulation of hepcidin is a primary target, with hepcidin antagonists (e.g., PTG-300) in Phase II trials designed to restore iron mobilization by obstructing hepcidin's suppression of ferroportin [31]. Anti-inflammatory approaches, such as IL-6 inhibitors, may indirectly reduce hepcidin levels. In contrast, ERFE mimetics are being investigated to promote natural hepcidin suppression. A key focus of current research is studying patients with concurrent iron overload and functional deficiency. This research aims to assess the efficacy of precision chelation (e.g., deferasirox modified through NTBI monitoring) and erythropoiesis-stimulating drugs (ESAs) such as Luspatercept (Reblozyl), which are designed to enhance hemoglobin synthesis without increasing iron toxicity. Furthermore, antioxidant therapy (e.g., Nrf2 activators) may alleviate iron-induced oxidative stress, providing a multifaceted strategy to address SCD-related iron dysregulation [32].

7. Clinical Implications and Future Directions

Incorporating innovative biomarkers, such as reticulocyte hemoglobin (Ret-He), ERFE, and NTBI, into clinical practice can transform the assessment of iron status in SCD. This transformation goes beyond the constraints of ferritin and transferrin saturation. The future of management may see the integration of personalized algorithms. These algorithms would combine hepcidin-targeted medicines for functional iron shortage with customized chelation for overload. This approach would be guided by sophisticated imaging techniques (e.g., MRI-LIC) and dynamic iron trafficking assays, highlighting the role of advanced technology in future management [27 – 29]. Research priorities encompass the validation of ERFE as a predictive biomarker for hepcidin response and the optimization of combinatorial regimens, such as erythropoietin-stimulating agents (ESAs) combined with intravenous iron, in specific patient populations. Long-term objectives encompass the mitigation of vaso-occlusive crises and end-organ damage by addressing iron's dual role in anemia and oxidative stress, thereby enhancing the quality of life in SCD.

8. Conclusion

Patients with SCD have intricate iron homeostasis, which requires careful evaluation of iron indices. While ferritin and TSAT are commonly used, LIC measured through MRI and sTfR improve diagnostic accuracy. The potential of future therapies aimed at regulating hepcidin is significant, offering the promise of enhanced iron management for individuals with sickle cell disease.

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