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Iron metabolism and genetic modifiers in thalassemia and sickle cell anemia

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Abstract

Iron metabolism plays a crucial role in the management of hemoglobinopathies, particularly in conditions such as β-thalassemia and sickle cell disease (SCD). This paper reviews briefly the present knowledge of iron overload in patients with transfusion-dependent thalassemia (TDT), non-transfusion-dependent thalassemia (NTDT), and SCD, highlighting the distinct paths leading to iron accumulation in each condition. The primary focus of this review is on the role of known genetic modifiers that influence iron metabolism and the variability in iron overload presentation among those patients. Genetic pathogenic variants in genes such as *HFE*, *HRFE*, *HAMP*, *TFR2*, *SLC40A1*, and others significantly impact iron regulation. These modifiers can exacerbate or ameliorate iron overload. Better understanding the role of those (and other) genetic factors is important for explaining the diverse disease severity and differences in the mechanism and clinical presentation of iron overload in these patients. The ongoing the International Hemoglobinopathy Research Network (INHERENT) study aims to further elucidate the influence of these (and other) unknown genetic modifiers through a comprehensive genome-wide association study. This project can potentially lead to novel therapeutic interventions for managing iron homeostasis in patients with hemoglobinopathies.

Keywords: *iron, iron metabolism, iron overload, thalassemia, sickle cell disease, hepcidin, hemojuvelin, erythroferrone, transferrin receptors, ferroportin*

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1. Introduction

Iron is an essential element for various physiological processes, particularly in respiratory function, as it is a critical component of hemoglobin. However, the delicate balance of iron homeostasis must be maintained, as both iron deficiency and iron excess can have detrimental effects on cellular function [1]. In the context of β-thalassemia and sickle cell disease (SCD), a group of inherited hemoglobin disorders, patients are susceptible to iron overload, albeit through distinct mechanisms [2]. In β-thalassemia, we recognize two groups of patients, transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT). In SCD there are also two groups of patients, patients homozygous for the Hgb S gene (sickle cell gene—*HBB.c:20T>A*) and patients with double heterozygous or bi-allelic carriers like sickle cell β-thalassemia and other rarer combinations of the sickle cell gene and hemoglobin C (*HBB c:19G>A*), D (*HBB c:364G>C*) or O Arab (*HBB:c.364G>A*) genes. For the issue of iron overload, all SCD patients are referred together in spite of the fact that there are some minor differences between them.

TDT patients develop iron overload initially by increased absorption due to the onset of dyserythropoiesis, but mainly due to the required frequent blood transfusions, which become essential to compensate for the inadequate production of functional hemoglobin. With each transfusion, these patients receive donor-derived red blood cells (RBCs) that contain significant amounts of iron. Over time, excess iron accumulation from transfused RBCs exceeds the capacity to utilize or eliminate it, a capacity that is minimal, resulting in iron overload [3, 4]. This chronic iron overload can lead to iron deposition in various critical organs and tissues, causing damage to their structure and function [5, 6].

In contrast, iron overload in NTDT patients arises primarily from the unique pathophysiology of ineffective erythropoiesis [2, 7]. Ineffective erythropoiesis refers to the impaired production and premature destruction of RBCs in thalassemia, leading to increased iron absorption from the gastrointestinal tract. The underlying molecular mechanisms triggering this dysregulation are

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multifactorial and complex [8–10]. Insufficient production of normal hemoglobin in NTDT causes an imbalance in the α-to-non-α globin chain ratio, resulting in excess free α-globin chains. These free α-globin chains precipitate within the developing RBCs, leading to ineffective erythropoiesis, increased iron absorption, and subsequent iron overload [11–13].

Given the propensity for iron overload in both TDT and NTDT, iron chelation therapy is a vital component of thalassemia management. Iron chelators are pharmacological agents that bind to excess body iron in stable complexes that can be eliminated through urinary and fecal excretion. These chelators help in preventing iron accumulation in vital organs such as the heart, liver, and endocrine glands, mitigating the associated complications and improving patient outcomes.

On the contrary, patients with SCD and either homozygous SCD or biallelic sickle cell β-thalassemia usually do not develop clinical features of iron overload [14, 15].

There is a group of SCD patients that require regular blood transfusions for several indications. Those patients may develop iron overload, and then they also require the use of iron chelators [15].

2. Methods

In this review, we summarize the actual knowledge on iron regulation and metabolism in patients with hemoglobinopathies. Special emphasis is placed on the description of known or possible genetic regulators of the factors that can affect iron status in those patients. In order to perform the review, we searched the literature using PubMed and Google Scholar and selected the most relevant papers based on the authors' expertise.

3. World incidence and prevalence of hemoglobinopathies

Hemoglobinopathies are the most common genetic disorders worldwide [16, 17]. In a report that summarized the number of β-thalassemia patients born each year, the figure is up to 40,000 new patients born yearly; this is based on the data collected in 2018 by the World Health Organization. Most of those patients are TDT (63%) and just one third are NTDT patients. We need to remember that an NTDT patient can become TDT at an older age. Evidently, the vast majority of new patients are born in Asia and around the Mediterranean basin where β-thalassemia was originally spread. In recent years, due to population migration, β-thalassemia is present in significantly low numbers in non-Mediterranean countries of Europe [16]. The carriers' rates are from less than 1% up to more than 10% in Mediterranean countries. In some Arab countries, up to 35% carriers' rate were reported; however, those reports were regional or local.

The incidence of α-thalassemia carriers is more frequent in southeast Asia and probably also in the Western world, but no systematic carrier screening has been performed since the clinical significance of α thalassemia in the Western world is low or even not present. It is accepted that about 5% of the world's population carries a gene defect.

Sickle cell disease is more common than β-thalassemia; about 300,000 new patients are born each year, and most of them in African countries [18]. Due to slave trade and migration, currently, SCD patients are spread all over America, the Middle East, India and European countries.

4. The regulation of iron homeostasis

Iron absorption in the intestine is an active process involving several tightly regulated steps. Initially, dietary iron exists predominantly in the ferric (Fe^{3+}) state, which is reduced to the more soluble ferrous (Fe^{2+}) form by the enzyme ferric reductase on the apical surface of enterocytes. Ferrous iron is then transported into intestinal epithelial cells via the divalent metal transporter 1 (DMT1). Once inside the cell, iron can be stored or exported into the bloodstream, where it is oxidized back to the ferric form (Fe^{3+}) and binds to transferrin for systemic distribution. Hemojuvelin (HJV), encoded by the *HJV* gene, plays a critical regulatory role in this pathway, particularly in modulating hepcidin expression. Cellular uptake of transferrin-bound iron is mediated by transferrin receptors, primarily encoded by the transferrin receptor 1 gene (*TFRC*). Systemic iron homeostasis is chiefly regulated by hepcidin, a peptide hormone produced in hepatocytes under the control of the bone morphogenetic proteins and human homologues of the Drosophila Mad (BMP/SMAD) signaling pathway and encoded by the *HAMP* gene. Hepcidin inhibits iron export by binding to and inducing the internalization of ferroportin, a cellular iron exporter. During increased erythropoietic demand, hepcidin expression is suppressed, facilitating greater iron absorption; conversely, inflammatory states upregulate hepcidin, reducing iron uptake.

In β-thalassemia, iron regulation is predominantly influenced by ineffective erythropoiesis rather than by iron overload per se [19]. Additionally, erythroferrone, a cytokine produced by erythroblasts and encoded by the erythroferrone gene (*ERFE)*, acts as a key suppressor of hepcidin during heightened erythropoietic activity, further promoting iron absorption. Erythroferrone is secreted by erythroblasts in response to erythropoietin (EPO) [20]. This increases iron absorption and mobilization to support erythroid expansion but can drive iron overload when erythroferrone is chronically high. In β-thalassemia, ineffective erythropoiesis drives high erythroferrone and profound hepcidin suppression, causing severe iron overload even without transfusion [21]. In thalassemic mice, erythroferrone overexpression further aggravates hepcidin inhibition and organ iron loading, whereas erythroferrone deletion normalizes hepcidin and mitigates iron overload. By contrast, transfusion-dependent thalassemia patients show suppressed EPO/ERFE and relatively increased hepcidin after transfusion [22]. Sickle cell disease also features elevated erythroferrone from chronic anemia, but concomitant inflammation (e.g., high IL-6) blunts hepcidin suppression. Some studies report that heavily transfused SCD patients have high erythroferrone linked to low hepcidin and iron loading [23], yet overall SCD hepcidin/ferritin ratios are higher than in thalassemia, implying multifactorial regulation. Thus, erythroferrone contributes to anemia-driven hepcidin suppression in both conditions, but its impact on iron loading is modulated by transfusion and inflammatory status (**Figure 1**).

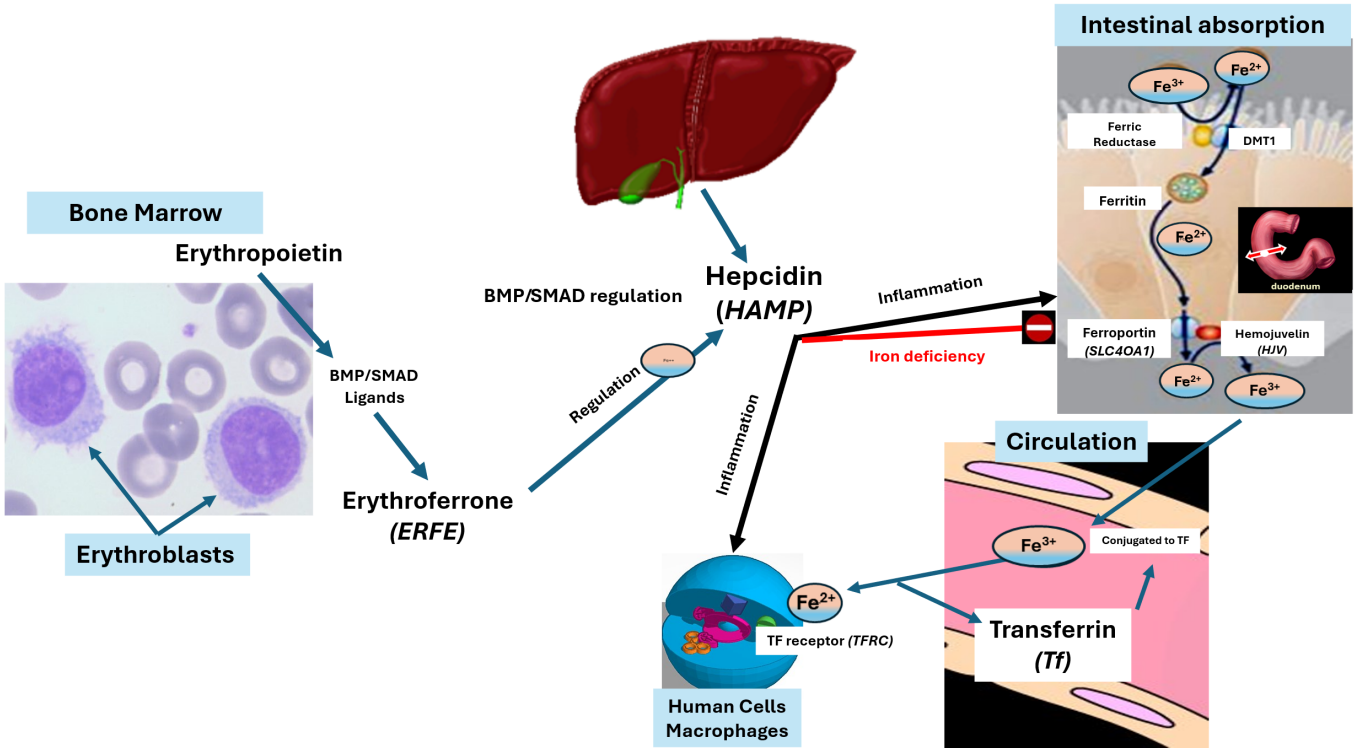

Figure 1 • Iron homeostasis. Abbreviations: Tf: transferrin; *ERFE*: erythroferrone gene; *HAMP*: hepcidin gene; *TFRC:* transferrin receptor 1 gene; *SLC40A1*: ferroportin gene (also known as solute carrier family 40 member 1); *HJV*: hemojuvelin gene; BMP: bone morphogenetic protein; SMAD: human homologue of the Drosophila Mad; DMT1: divalent metal transporter 1.

5. Evaluation of iron overload

The most frequently used analysis for iron overload evaluation is serum ferritin, with all the known limitations of this analysis, principally being ferritin affected by inflammatory processes. Serum transferrin saturation over 70 or 80% can predict the appearance of serum-free iron, the non-transferrin bound iron (NTBI), that is absorbed into the cells and stored as ferritin. Direct analysis of free serum iron can be evaluated by the level of NTBI or labile plasma iron (LPI) [24].

Currently, the gold standard for iron overload evaluation is T2* Magnetic Resonance Imaging. This procedure can assess iron deposition in the heart, liver and pancreas [25].

6. Genetic modifiers in hemoglobinopathies

The severity of anemia and the extent of iron overload can vary widely among patients with hemoglobinopathies, even within the same subtype. This variability is attributed, at least in part, to genetic modifiers that influence iron metabolism. Genetic modifiers exert a significant influence on the variable manifestations of iron overload among those patients. Unraveling these modifiers is of the utmost importance as it can aid in identifying individuals who are at a higher risk of developing iron overload and guide personalized treatment strategies [10].

Several genes involved in iron metabolism including those encoding human homeostatic iron regulator protein (*HFE*), transferrin (TF), transferrin receptor 2 (*TFR2*), ferroportin (*SLC40A1*), hepcidin (*HAMP*), *HJV*, glutathione S-transferases (*GST*) and ceruloplasmin (*CP*) have been described as genetic modifiers of metabolic iron disorders [14, 15]. By leading to hemochromatosis, which is characterized by excessive dietary iron absorption and iron accumulation, pathogenic variants on the *HFE*, *HJV*, *HAMP*, *TFR2* and *SLC40A1* genes could aggravate already existing iron overload in thalassemia patients [26, 27]. Genetic variations of the *GST* genes, however, exhibited a high association with the deposition of iron specifically in cardiac tissue. Among *GST* family members, glutathione S-transferase M1 (*GSTM1*) and glutathione S-transferase T1 (*GSTT1*) null polymorphisms are the most consistently associated with cardiac iron deposition in β-thalassemia major [28]. Variations on *TMPRSS6*, *TF*, *CP* and ferritin light chain (*FTL*) genes were also associated with either high serum ferritin levels or iron accumulation in specific tissues such as the liver, pancreas, heart, and basal ganglia [29, 30].

A summary of the most described genetic modifiers is presented in **Table 1** and **Figure 1**.

Table 1 • Summary of the genetic modifiers of iron metabolism in thalassemia and sickle cell disease.

Gene	Encoded protein/function	Key variants or polymorphisms	Evidence in β-thalassemia/SCD	Organ-specific iron association	Evidence
HFE (human homeostatic iron regulatory gene)	Regulator of transferrin receptor signaling and hepcidin expression	*C282Y*, *H63D*	Associated with increased ferritin and hepatic iron in thalassemia; limited data in SCD	Liver predominance	[28]
HAMP (Hepcidin gene)	Hepcidin, master inhibitor of ferroportin-mediated iron export	Promoter variants (e.g., *c.-582 A>G*)	Linked to reduced hepcidin and higher iron burden in thalassemia; scarce SCD data	Systemic/hepatic	[19]
TFR2 (Transferrin receptor 2 gene)	Hepatic transferrin receptor regulating hepcidin via BMP pathway	Loss-of-function and polymorphic variants	Contributes to iron overload biology; modifier role in thalassemia incompletely defined; minimal SCD evidence	Liver and systemic iron regulation	[27]
SLC40A1 (Ferroportin gene)	Ferroportin iron exporter	*Q248H*, *Val162del*	Altered iron export and inflammatory associations in SCD; inconsistent ferritin association in NTDT	Reticuloendothelial system and liver	[31]
HJV (Hemojuvelin gene)	BMP co-receptor regulating hepcidin transcription	*I222N* and others	Associated with severe iron loading and cardiac deposition in thalassemia	Cardiac and hepatic	[31]
GSTM1/GSTT1 (glutathione S-transferases gene, M1 and M2 variants)	Detoxification enzymes modulating oxidative stress	Null polymorphisms	Repeatedly associated with cardiac iron overload in β-thalassemia; very limited SCD evidence	Cardiac predominance	[29]
CP (Ceruloplasmin gene)	Ceruloplasmin ferroxidase in iron export	Loss-of-function variants	Rare contribution to systemic iron dysregulation; unclear modifier role in hemoglobinopathies	Brain and liver (systemic hemosiderosis)	[30]
TMPRSS6 (tumor-associated membrane protein gene, variant RSS6)	Matriptase-2, negative regulator of hepcidin	*A736V* and others	Influences ferritin and hepatic iron in iron-loading states; modifier role in thalassemia under study	Hepatic	[31]

Abbreviations: SCD: sickle cell disease; NTDT: non-transfusion-dependent thalassemia; BMP: bone morphogenetic protein.

6.1. High Fe (*HFE*) gene

The *HFE* gene, located on chromosome 6p21.3, encodes a protein involved in regulating iron homeostasis [32]. The High Fe (HFE) protein interacts with transferrin receptor 1 (TfR1) and plays a crucial role in the sensing and regulation of iron absorption from the intestinal epithelium [33]. Through its interaction with TfR1, the HFE protein modulates the expression of hepcidin, a key hormone that regulates iron absorption and recycling [34]. Pathogenic variants in the *HFE* gene are known to cause hereditary hemochromatosis, a disorder characterized by excessive iron absorption and deposition in various organs, including the liver, heart, and pancreas. The most common *HFE* pathogenic variants are *C282Y* and *H63D*, which have been extensively studied in various populations. In Mediterranean populations, the *C282Y* variant is low, 1 to 5%, compared to more than 7% in European populations [35].

The presence of *HFE* gene pathogenic variants in thalassemia patients has important clinical implications. It can serve as a predictive marker for the development of iron overload and help identify individuals who may require more aggressive iron chelation therapy. Regular monitoring of iron parameters, such as serum ferritin levels and transferrin saturation, along with genetic testing for *HFE* gene pathogenic variants, can aid in risk stratification and personalized management of iron overload in thalassemia patients. The effect of *HFE* pathogenic variants on iron metabolism in thalassemia patients is complex and may depend on several factors, including the type of thalassemia, the age of the patient, and the frequency and duration of transfusions [27]. The presence

of *HFE* pathogenic variants was associated with increased serum ferritin levels, a marker of iron overload, in beta-thalassemia carriers and a higher risk of developing hepatic iron accumulation in NTDT patients, whereas the literature mostly shows no significant association between *HFE* pathogenic variants and serum ferritin levels in thalassemia major patients who were regularly chelated [26].

The mechanisms by which *HFE* gene pathogenic variants contribute to iron overload in thalassemia are not fully understood. However, it is believed that these pathogenic variants affect the regulation of hepcidin, the master regulator of iron homeostasis [32–34]. The *C282Y* pathogenic variant has been shown to disrupt the interaction between *HFE* and TfR1, leading to reduced hepcidin production [32]. Decreased hepcidin levels result in enhanced iron absorption from the gastrointestinal tract, leading to iron overload in thalassemia patients with *HFE* gene pathogenic variants [36]. TfR1 hepatocyte regulation of hepcidin required *HFE* [37]. A recent investigation into the influence of the *HFE* gene on liver iron accumulation in individuals with SCD found that those harboring a pathogenic variant of the *HFE* gene and undergoing chelation therapy exhibited greater liver iron deposition than patients without the pathogenic variant [38].

6.2. Hepcidin gene (*HAMP*)

Hepcidin is a key regulator of iron homeostasis. It controls body iron levels by modulating iron absorption in the small intestine and iron release from macrophages [36]. The *HAMP* gene, located on chromosome 19q13, encodes pre-prohepcidin, which is processed into the biologically active hormone hepcidin. Hepcidin acts by binding to ferroportin, the iron exporter protein, leading to its internalization and degradation, thereby inhibiting iron release from enterocytes and macrophages [31]. Dysregulation of hepcidin production is often associated with genetic variations in the *HAMP* gene and can disrupt iron balance and contribute to iron overload in thalassemia patients [39].

Several *HAMP* gene variants have been identified and associated with alterations in hepcidin levels and iron metabolism [40]. One such variant is the *HAMP* c.-582 A>G polymorphism, which has been linked to decreased hepcidin expression and increased iron absorption [41]. This polymorphism is more prevalent in thalassemia patients with iron overload, suggesting its role in influencing disease severity and iron burden [42]. In a study conducted by Andreani et al., it was revealed that the *c.-582 A>G* variant was correlated with liver iron overload and elevated serum ferritin levels in individuals with β-thalassemia major who had irregular chelation therapy [41]. Furthermore, Island et al. demonstrated that the *c.-153C>T* variant, located within a BMP-responsive element, decreased the basal expression of the hepcidin gene by impairing its response to BMPs and IL-6. By this way of action, lowering the hepcidin expression increased iron absorption and iron overload in those patients [43]. A recent study performed in a cohort of SCD patients showed the influence of the *HAMP* genotype [44].

In one study on SCD patients, serum hepcidin levels were found to be normal in all patients (17–286 ng/ml), irrespective of serum ferritin levels or the number of blood transfusions [45].

Low levels of hepcidin were found in transfusion-dependent β-thalassemia patients but not in SCD. Increased intestinal absorption may contribute to iron overload and high transferrin saturation present in transfusion-dependent β-thalassemia but not in SCD [35]. Therapeutic strategies aimed at modulating hepcidin levels and restoring iron balance are being explored. One potential approach is the use of hepcidin agonists, which mimic the action of hepcidin and promote iron sequestration, thereby reducing iron overload. Clinical trials investigating the efficacy and safety of hepcidin agonists in thalassemia patients are underway, with promising preliminary results [46].

6.3. Transferrin receptor 2 gene (*TFR2*)

Transferrin receptor 2 (TfR2), encoded by the *TFR2* gene located on chromosome 7q22, is a transmembrane glycoprotein expressed predominantly in hepatocytes [47]. It functions as a key regulator of iron homeostasis by interacting with transferrin and modulating iron uptake into cells. TfR2 forms a complex with the TfR1 on the cell surface, facilitating the internalization of transferrin-bound iron into hepatocytes. Through its association with hemojuvelin and the bone morphogenetic protein (BMP) signaling pathway, TfR2 influences the production of hepcidin, a hormone that regulates iron absorption and recycling [48].

Studies have shown that *TFR2* pathogenic variants or dysregulation is associated with iron overload [49, 50]. Disruption of TfR2 function affects the interaction with HJV and impairs the BMP signaling pathway, resulting in decreased hepcidin production. Reduced hepcidin levels lead to increased iron absorption from the intestine and enhanced release of iron from macrophages, exacerbating iron overload in thalassemia [36].

A recent murine model of *TFR2* deletion in TDT significantly ameliorated anemia and improved erythroid differentiation and RBC morphology, leading to an overall reduction in transferrin saturation and serum iron in bone marrow, likely due to increased iron consumption by improved erythropoiesis [51]. Iron content in the liver, spleen, kidney, and heart, along with hepatic expression of TfR1 and iron-responsive bone morphogenetic protein 6, however, remained unchanged. Another study showed no significant difference in ferritin levels and transferrin saturation between NTDT patients with and without *TFR2* polymorphisms (Exon 5 *I238M C>G, IVS16 +251 CA* deletion) [52].

Despite the evidence on *TFR2* pathogenic variants leading to hemochromatosis, the literature is scarce on the role of these pathogenic variants in thalassemia and SCD, and it is unclear if they could exacerbate or, on the contrary, ameliorate existing iron overload in these patients.

6.4. Ferroportin gene (*SLC40A1*)

SLC40A1 has a role in regulating iron homeostasis by encoding the transmembrane protein ferroportin (also known as solute carrier family 40 member 1 (*SLC40A1*) or iron-regulated transporter 1 (*IREG1*)), which is responsible for exporting iron from cells into the bloodstream [10]. In thalassemia, disruptions in the function of ferroportin can contribute to iron overload. Studies have reported that certain pathogenic variants or variants in the ferroportin gene are associated with altered iron transport, leading to increased iron accumulation in various tissues [31]. These genetic modifications can impact ferroportin expression, stability, or activity, resulting in impaired iron export and subsequent iron overload in thalassemia patients. On the other hand, a small study

on thalassemia intermedia (NTDT) and S/β-thalassemia patients reported no association between the *Val162del* pathogenic variant of the *SLC40A1* gene and serum ferritin levels [53].

A ferroportin *Q248H* variant, a variant that causes intracellular iron accumulation, was found in a group of fourteen SCD patients. Those patients had significantly higher levels of interleukin-6 and C-reactive protein compared to a group of patients that did not show this pathogenic variant. This finding may suggest that this variant may affect not only iron overload in SCD patients but also the known inflammatory status present in SCD [54].

Considering the importance of ferroportin in iron regulation, modulating its activity has emerged as a potential therapeutic strategy in thalassemia. By targeting ferroportin modulation, these therapeutic interventions aim to restore proper iron balance and mitigate iron overload complications in thalassemia patients. While the role of ferroportin in iron metabolism is evident and the potential of ferroportin modulation as a therapeutic target in thalassemia shows promise, the evidence regarding the association between *SLC40A1* expression and iron overload remains limited.

6.5. Other genes that affect iron metabolism

Furthermore, other genetic modifiers have also been implicated in iron overload in thalassemia. Variations in genes encoding proteins involved in iron transport and storage, such as *HJV*, *GST*, and *CP*, have been associated with altered iron metabolism and an increased risk of iron overload in thalassemia patients. These genetic modifiers affect iron absorption, cellular iron export, and the breakdown of heme, collectively influencing the overall iron balance.

Pathogenic variants in the *HJV* gene have been associated with juvenile hemochromatosis, a rare form of iron overload disorder. In thalassemia, certain *HJV* gene polymorphisms have been linked to altered hepcidin levels and iron overload. For example, the *HJV* I222N (AA) genotype is associated with significantly higher cardiac iron overload in thalassemia patients [31]. These polymorphisms may contribute to the dysregulation of hepcidin and the disruption of iron homeostasis in thalassemia.

Glutathione S-transferases are a family of enzymes involved in the detoxification of xenobiotics and oxidative stress [55]. *GST* polymorphisms have been implicated in susceptibility to various diseases, including iron overload in thalassemia [55]. *GST* gene polymorphisms may influence the antioxidant capacity and detoxification processes, leading to imbalanced iron homeostasis and iron accumulation in thalassemia. Certain *GST* gene variants like *GSTM1* and *GSTT1* have been associated with higher serum iron and ferritin levels, as well as liver and cardiac iron deposition in thalassemia patients [56].

Ceruloplasmin is a copper-binding protein involved in iron metabolism and oxidative stress regulation [30]. Genetic variations in the *CP* gene have been associated with alterations in ceruloplasmin activity and iron overload [30, 57]. These gene variants may affect the antioxidant properties of ceruloplasmin and disrupt its role in iron metabolism, contributing to iron overload in thalassemia.

Understanding the impact of these gene polymorphisms on iron metabolism in thalassemia patients has important clinical implications. Identification of these genetic variations can help predict disease severity, assess the risk of iron overload, and guide personalized treatment strategies. Therapeutic interventions, aimed at modulating the expression or activity of these genes, may offer potential avenues to restore iron homeostasis and mitigate iron-related complications in thalassemia. Further research is needed to elucidate the functional significance of these gene polymorphisms and their precise role in iron metabolism dysregulation in thalassemia. Despite an abundance of genes known to be associated with iron metabolism and iron-related disorders, there is not enough evidence of their implication in thalassemia except for several *HFE* polymorphisms. In SCD, studies on the effect of those genes on iron metabolism are even rarer. This, in fact, necessitates a genome-wide association studies (GWAS) of a large caliber to reveal existing associations specifically in patients with hemoglobinopathies.

7. Clinical studies related to iron overload in SCD patients

Few studies analyzed the clinical features of iron overload in SCD patients. All those studies showed that even regularly transfused SCD patients did not develop severe iron overload clinical features as in transfusion-dependent β-thalassemia. This issue requires more research in larger cohorts. We found it important to describe some studies reported in the literature.

In a study published by Vichinsky et al., organ dysfunction in β-thalassemia and SCD was compared. In that study, no cardiac or endocrine disease was found among SCD patients despite similar ferritin levels. In another study by the same group, no significant difference in clinical complications of iron overload was found between transfused and non-transfused SCD patients [14].

In a more recent study performed by Badaw, moderate to severe transfusional iron overload in SCD was not associated with abnormal cardiac function based on echocardiogram or serum biomarkers [58].

7.1. Iron overload imaging studies in SCD patients

Cardiac iron measurements in SCD, studied by T2* MRI, showed no indication of significant myocardial siderosis and no correlation between serum ferritin and cardiac iron content [59, 60].

In another study, six out of ten patients with sickle/β^0-thalassemia demonstrated evidence of liver iron overload, with variable severity (<6.3 ms). No heart iron deposition was found in those patients [45].

7.2. Iron metabolism studies in SCD

The metabolic status of iron overload in SCD has been investigated in a limited number of laboratory studies. In our cohort analysis (Koren et al. [15]), none of the 36 SCD patients exhibited clinical manifestations of iron overload, despite the absence of continuous or regular iron chelation therapy. Notably, only two individuals demonstrated non-transferrin-bound iron (NTBI) values within the borderline range (0.4 units), with no cases of elevated NTBI. LPI was detected in only one patient. These findings indicate that iron status parameters in SCD patients, even following frequent transfusions, differ substantially from those observed in thalassemia [15]. The consistently low NTBI and LPI levels in

SCD are consistent with the lack of clinical evidence for iron overload in this population. Subjects with SCD may be protected from iron-related toxicity because of their chronic inflammatory state resulting in potentially less toxic accumulation of iron in macrophages [61].

Supporting these observations, an independent study reported undetectable levels of LPI and NTBI in all ten patients with sickle/β^0-thalassemia [45].

Badawy et al. demonstrated that SCD patients undergoing chronic transfusion therapy did not develop significant cardiac iron accumulation, regardless of serum ferritin concentrations, hepatic iron content as assessed by T2* MRI, or the degree of erythropoiesis suppression [58].

8. Conclusions

The parameters of iron status in SCD patients, even after frequent transfusions, are different when compared to patients with β-thalassemia.

Several genes related to iron-regulated gene expression were analyzed and summarized in this review. An association with inflammasome complex pathway genes like NLR family pyrin domain containing 3 (*NLRP3*), NLR family CARD domain containing 4 (*NLRC4*), and caspase 1 (*CASP1*) was demonstrated. This supports Pippard's theory that in SCD, inflammation may prevent iron overload.

Analyzing different genes that are involved in iron homeostasis and inflammation in a very large group of SCD patients, and comparing them with the expression of the same genes in NTDT and TDT β-thalassemia patients can add new data and understanding for the interpretation of iron homeostasis, and probably for the development of new drugs that may prevent, or treat, iron overload in those patients.

The ongoing INHERENT study (NCT05799118) intends to analyze the genetic modifiers in patients with hemoglobinopathies through a large, multi-ethnic genome-wide association study (GWAS). Such modifiers may explain not only diverse disease severity but also the differences in iron overload or iron metabolism, not only between different diagnoses but also between patients with the same initial genetic diagnosis such as TDT, NTDT, SCD and other hemoglobin disorders.

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Conceptualization, G.A. and A.K.; methodology, G.A., A.S. and A.K.; data curation, G.A., A.S. and A.K.; writing—original draft preparation, G.A., A.S. and A.K.; writing—review and editing, G.A., C.L., A.S., S.P., L.L. and A.K.; visualization, A.K.; supervision, G.A. and A.K. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

G.A., C.L., S.P. and A.K. are researchers at the INHERENT study group. G.A. is the Head of the Azerbaijan authors team. A.K. is the Head of the Israeli authors team. The authors declare that they have no other competing interests.

Data availability statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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