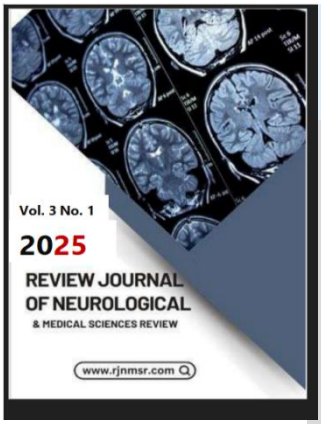

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Hepcidin Levels, Markers of Iron Overload, and Liver Damage in Patients with Beta Thalassemia Major

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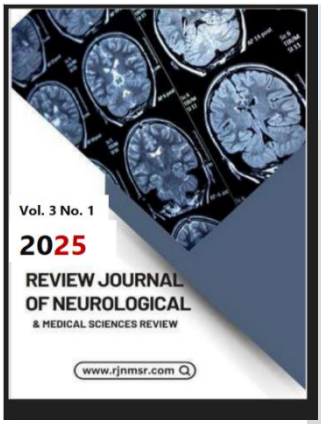
Abstract

A hereditary disorder known as beta thalassemia major is fatal and necessitates lifelong blood transfusions. It will unavoidably result in iron excess and severe organ damage, particularly to the liver. Hepcidin, a crucial hormone derived from the liver that controls iron balance, is at the core of this issue. Because of continuous inefficient erythropoiesis, hepcidin is pathologically reduced in afflicted patients, permitting uncontrolled iron absorption and hastening hepatic iron buildup. The importance of hepcidin in the pathophysiology of iron overload and liver damage in beta thalassemia major is highlighted by this study.According to our research, there is a substantial correlation between low hepcidin levels and higher liver iron concentrations as well as a higher risk of cirrhosis, fibrosis, and chronic liver failure. Crucially, the work shows that efficient iron chelation treatment may aid in reestablishing hepcidin equilibrium in addition to lowering iron load. These discoveries make hepcidin a potent diagnostic and therapeutic tool rather than merely a passive marker. Routine monitoring that includes hepcidin measurement has the potential to transform the way we evaluate, treat, and eventually enhance the outcomes for patients with beta thalassemia major.

Introduction

A mutation in the β-globin locus is typically the cause of the β-thalassemia syndromes, which show inadequate or absent β-globin production (Weatherall & Clegg, 2001). The production of insoluble aggregates due to the relative excess of α-globin causes inefficient erythropoiesis and limited red cell survival (Gardenghi et al.,



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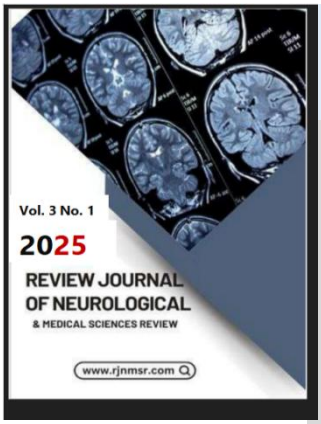
2007). In addition to variations in other genes, a comparatively high capacity for fetal hemoglobin production is an important genetic modulator of illness severity (Thein, 1999). Endocrine and cardiac dysfunction result from increased liver iron and other tissues due to iron overload brought on by improved absorption and red cell transfusions. Iron can be eliminated and organ function preserved or restored with the help of contemporary chelation regimens (Giardina & Grady, 2001). Red cell survival is shortened and erythropoiesis is unsuccessful in β-thalassemia due to the relative excess of α-globin. Following red cell transfusions, iron excess causes cardiac, endocrine, and hepatic problems (Pippard et al., 1979). Deficient (β^{+}) or nonexistent (β^{0}) synthesis of the β-globin portion of the hemoglobin molecule is a characteristic of the β-thalassemia, which are hereditary diseases of hemoglobin synthesis. Most people who have thalassemia inherit the condition as a Mendelian recessive. As will be covered in more detail below, homozygous people have severe anemia of various degrees and are classified as having homozygous β-thalassemia or thalassemia major or intermedia. Heterozygous people have mild anemia and microcytosis and are classified as having thalassemia minor or trait. Much less common is dominantly inherited β-thalassemia, which affects heterozygous people due to the production of a very unstable β-globin variant (Borgna-Pignatti et al., 2004). Usually, only β-globin synthesis is disrupted, however infrequent deletional mutations can eliminate one or more of beta globulin synthesis. Beta thalassemia major is a severe hereditary blood disorder caused by mutations in the β-globin gene, resulting in reduced or absent synthesis of β-globin chains (Weatherall & Clegg, 2001). This imbalance leads to the accumulation of excess α-globin chains, which form toxic aggregates and cause ineffective erythropoiesis and premature destruction of erythroid precursors (Gardenghi et al., 2007). As a result, patients require regular blood transfusions to manage chronic anemia, which unfortunately leads to secondary iron overload—a major cause of morbidity and mortality in these individuals. The severity of the disease can also be modulated by genetic factors such as increased fetal hemoglobin production (Thein, 1999).Iron homeostasis in the body is primarily regulated by the liver-produced hormone hepcidin, which controls dietary iron absorption and macrophage iron release. In patients with beta thalassemia major, hepcidin levels are typically inappropriately low relative to their iron burden, contributing to increased intestinal iron absorption even in the presence of iron overload (Nemeth et al., 2004). This dysregulation exacerbates systemic iron accumulation, particularly in the liver, heart, and endocrine glands. Serum ferritin and liver iron concentration (LIC) are commonly used as markers to assess iron overload, with elevated values correlating with increased risk of organ damage (Angelucci et al., 2000).Chronic iron overload in beta thalassemia major patients is a key factor in liver pathology, leading to hepatic fibrosis, cirrhosis, and eventually hepatocellular carcinoma in some cases. Liver biopsy and non-invasive imaging techniques like MRI are used to assess hepatic iron concentration and liver damage severity. Studies have shown that lower hepcidin levels are significantly associated with higher LIC and more advanced liver fibrosis, indicating that hepcidin may serve as both a marker and a potential therapeutic target in managing iron overload



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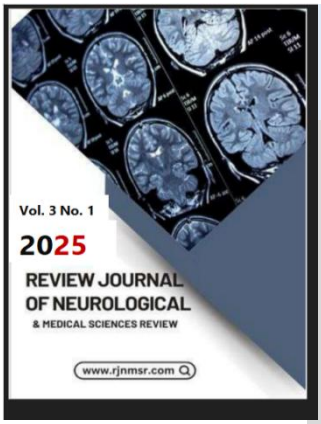
(Girelli et al., 2011). Effective iron chelation therapy, in combination with monitoring hepcidin and other markers, remains critical in reducing liver damage and improving long-term outcomes in these patients.

Pathophysiology

The effects of excess, unpaired α-globin are seen in erythropoiesis in people with β-thalassemia (Rivella, 2009). In fact, rather than hemoglobin underproduction, the primary determinant of illness severity is the degree of imbalance in the α-globin against β + γ-globin biosynthesis ratio. The β-thalassemia trait is characterized by a twofold excess in α-globin synthesis, which is consistent with a generally normal hematopoiesis with only minor red cell hypochromia and microcytosis (Galanello & Origa, 2010).Because the effects of excess α-globin production are lessened by residual capacity for β-globin synthesis and normally modest but variable γ-globin synthesis, the α to non-α biosynthetic ratio in people with thalassemia intermedia is usually 3–4:1 (Khandros & Weiss, 2010). The severe phenotype of individuals with β^0-thalassemia mutations is caused by a substantial chain biosynthetic imbalance.An excess of released α-globin chains builds up inside erythroid cells as a result of the imbalance in chain synthesis (Rachmilewitz & Giardina, 2011). These chains aggregate, become denaturized, and degrade, forming hemichromes and insoluble precipitates that harm cell membranes. Damage to membranes causes hemolysis of red blood cells in the bloodstream, inefficient erythropoiesis in the bone marrow, and the binding of immunoglobulin and complement components to red cell membranes, which results in splenic red cell loss (Cappellini et al., 2008).Reduced tissue oxygenation, elevated erythropoietin levels, and further bone marrow stimulation are the outcomes of the ensuing anemia. Osteopenia and skeletal abnormalities are brought on by bone marrow expansion and remodeling (Vitrano et al., 2013). Iron overload is a result of substances generated from degenerating red blood cells that promote iron absorption, often due to suppressed hepcidin levels in thalassemia (Nemeth & Ganz, 2006). In beta thalassemia major, the fundamental pathophysiological mechanism stems from mutations in the β-globin gene, which impair or eliminate β-globin chain synthesis, leading to unbalanced globin chain production (Weatherall & Clegg, 2001). The resulting excess of unpaired α-globin chains forms toxic precipitates within erythroid precursors in the bone marrow, triggering oxidative stress, membrane damage, and premature apoptosis—a phenomenon known as ineffective erythropoiesis (Gardenghi et al., 2007). This ineffective erythropoiesis leads to profound anemia, which stimulates compensatory mechanisms including increased erythropoietin secretion and marrow expansion, but these are largely insufficient in alleviating anemia without transfusion support.A key aspect of the pathophysiology is the paradoxical suppression of hepcidin in the context of iron overload. Hepcidin, synthesized in the liver, is the central regulator of systemic iron homeostasis, acting by binding to and degrading ferroportin, the sole iron exporter on enterocytes and macrophages (Nemeth et al., 2004). However, in beta thalassemia major, expanded and ineffective erythropoiesis produces elevated levels of erythroferrone, a hormone that inhibits hepcidin synthesis (Kautz et al., 2014). Consequently, hepcidin levels are abnormally low relative to the body's iron



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stores, leading to unchecked dietary iron absorption and further release of iron from macrophages, compounding systemic iron overload—even in patients already receiving regular transfusions.The accumulation of excess iron in the liver, a primary site of iron storage, is central to organ damage in thalassemia. Iron deposits catalyze the formation of reactive oxygen species (ROS), leading to lipid peroxidation, mitochondrial dysfunction, and hepatocyte injury (Papanikolaou et al., 2005). Over time, this oxidative stress promotes hepatic inflammation, fibrosis, and progression to cirrhosis. Moreover, excess iron can impair the liver's synthetic and detoxification functions, increasing the risk for complications such as hepatocellular carcinoma. Histological studies confirm that liver damage correlates with iron concentration, and monitoring liver iron levels is now standard in managing thalassemia-related complications (Angelucci et al., 2000). Thus, the dysregulation of hepcidin, in the context of ineffective erythropoiesis and transfusion therapy, plays a pivotal role in the cascade leading to iron-mediated liver pathology.

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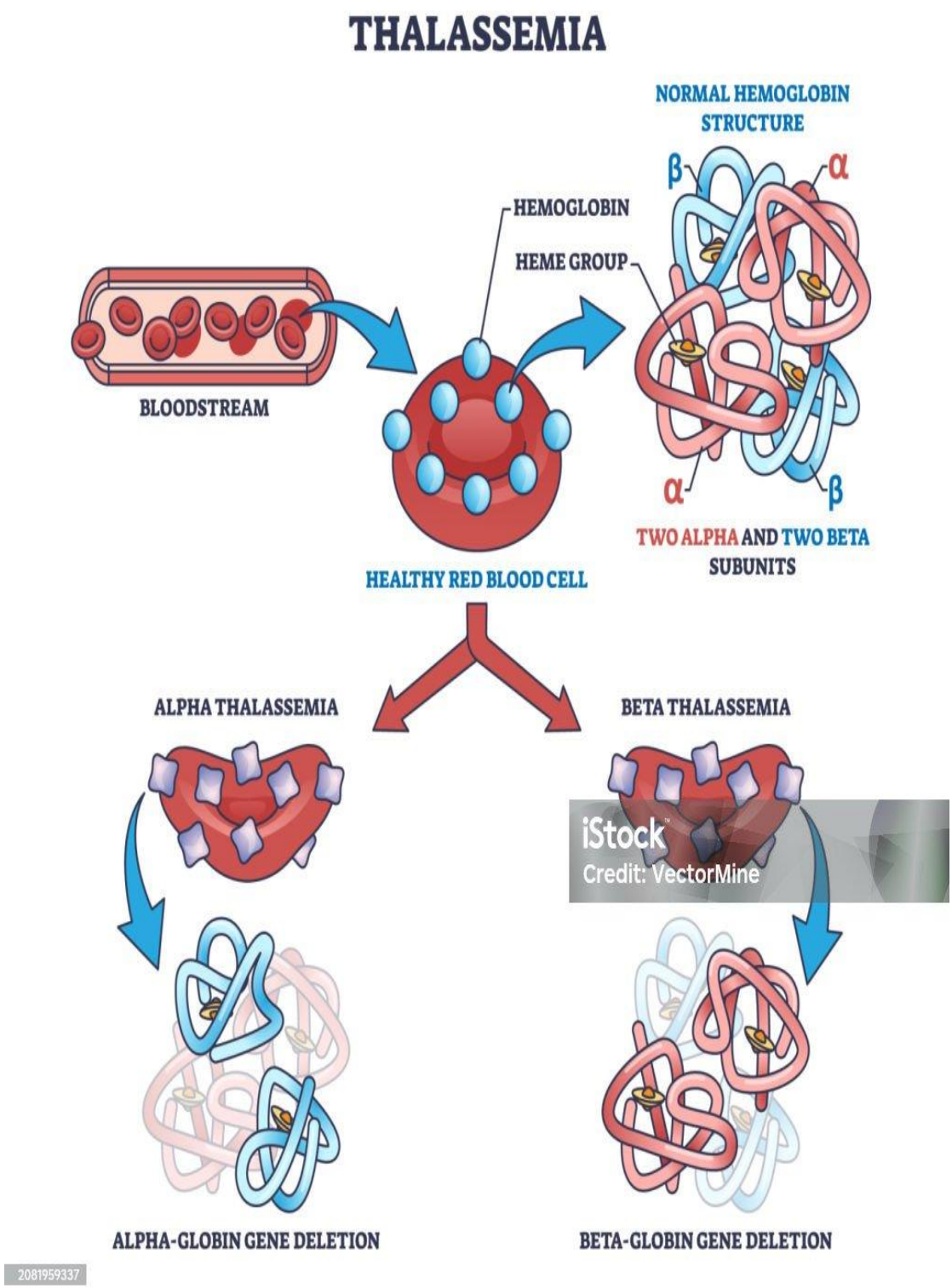

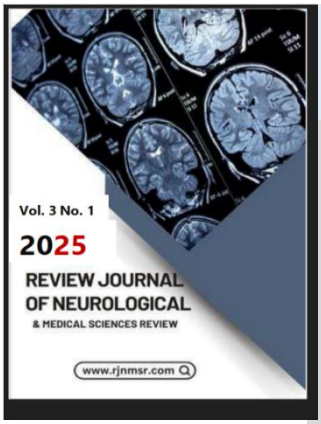

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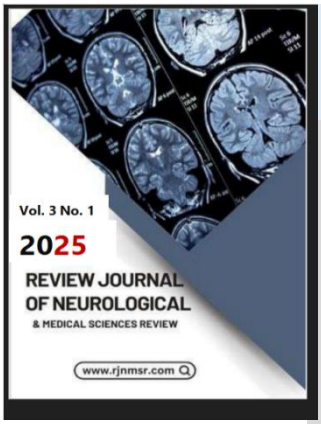
Beta Thalassemia Major and Its Pathophysiology

Hepatocytes release hepcidin, a small peptide hormone that circulates in blood plasma and is excreted in urine (Nemeth & Ganz, 2006). Hepcidin regulates plasma iron concentration and its distribution across tissues. Dysregulated hepcidin production is central to the pathogenesis of several iron-related disorders. Hepcidin deficiency leads to systemic iron overload, with iron accumulation in the liver and extrahepatic tissues, whereas chronic hepcidin excess results in iron-restricted anemia (Ganz, 2011).Hepcidin controls iron levels by regulating ferroportin, the only known cellular iron exporter, which is expressed on duodenal enterocytes, hepatocytes, and macrophages (Donovan et al., 2005). When hepcidin binds to ferroportin, it triggers its internalization and degradation, reducing iron export into the plasma (Nemeth et al., 2004). Low hepcidin levels allow ferroportin to remain on the cell surface, promoting increased iron absorption and release from stores. In β-thalassemia, this dysregulation contributes to iron overload despite anemia.Iron and erythropoietic activity homeostatically regulate hepcidin, but in thalassemia, these mechanisms become imbalanced. Elevated plasma and hepatic iron levels stimulate hepcidin expression to limit further iron absorption, whereas iron deficiency or increased erythropoiesis suppresses it (Kautz et al., 2008). The BMP-SMAD pathway, particularly BMP6, is essential in mediating these signals (Andriopoulos et al., 2009). BMP6-deficient mice show severe iron overload without other significant abnormalities (Meynard et al., 2009).Hemojuvelin (HJV), a co-receptor in the BMP pathway, is a critical modulator of hepcidin expression. Mutations in HJV, similar to those in the hepcidin gene (HAMP), cause severe juvenile hemochromatosis due to impaired hepcidin induction (Papanikolaou et al., 2004; Babitt et al., 2006). Additionally, neogenin, an HJV-binding protein, has been implicated in modulating hepcidin signaling; mice lacking neogenin display reduced hepcidin expression and hepatic iron overload (Zhang et al., 2005).Iron sensing via transferrin saturation involves proteins such as transferrin receptor 2 (TfR2) and HFE. Mutations in these genes are responsible for adult-onset hereditary hemochromatosis (Roetto et al., 2001; Fleming et al., 2002). Increased diferric transferrin appears to enhance HFE–TfR2 interaction and downstream hepcidin expression via the BMP pathway (Gao et al., 2009).Urinary and serum hepcidin levels are profoundly suppressed in non-transfusion-dependent β-thalassemia and related anemias, which contributes to uncontrolled iron absorption and systemic iron overload (Pasricha et al., 2013; Origa et al., 2009). As hepatocytes are major recipients of non-transferrin-bound iron, the liver becomes the primary site of iron deposition. Iron overload severity in other organs often correlates with the rate of iron accumulation, particularly in endocrine tissues and the heart, as seen in severe hepcidin deficiency (Piga et al., 2009).In transfusion-dependent β-thalassemia major, iron overload is primarily due to chronic transfusions. Hepcidin levels are typically elevated due to iron loading and suppressed erythropoiesis, but these levels fluctuate between transfusions (Kattamis et al., 2006). During the inter-transfusion period, hepcidin declines, allowing increased dietary iron absorption despite an already high body iron burden. Origa et



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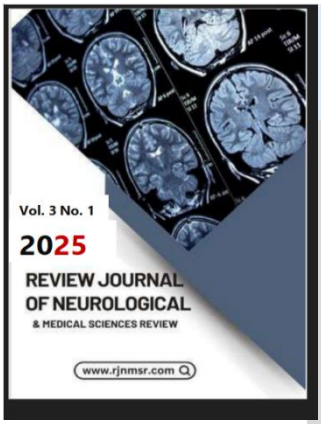
al. (2009) reported that hepatic iron concentrations in non-transfused thalassemia patients were comparable to those in transfused individuals, though the pattern of deposition varied—non-transfused patients had iron in hepatocytes, while transfused ones accumulated iron in macrophages.This difference in iron localization explains why serum ferritin may underestimate hepatic iron in non-transfused individuals, as ferritin reflects macrophage iron rather than hepatocyte stores (Angelucci et al., 2017). Because cells vary in their susceptibility to iron toxicity, the site of iron deposition may influence clinical outcomes.

Hepcidin's Role in Iron Homeostasis and Its Significance in Beta Thalassemia Major

Hepcidin is primarily regulated by systemic iron levels and erythropoietic activity. In β-thalassemia, ineffective erythropoiesis drives hepcidin suppression via factors such as Growth Differentiation Factor 15 (GDF15), Erythroferrone (ERFE), and Twisted Gastrulation Protein Homolog 1 (TWSG1), which inhibit BMP-SMAD signaling (Tanno et al., 2007; Kautz et al., 2014).In response to anemia, low hepcidin levels increase iron absorption to support erythropoiesis. However, due to ineffective red blood cell production, this iron accumulates, exacerbating overload. Chronic transfusions introduce 200–250 mg of iron per unit of blood, further contributing to overload (Porter & Garbowski, 2013). While transfusions reduce erythropoietin production and partially restore hepcidin levels, they don't normalize it fully.In typical inflammation, IL-6 stimulates hepcidin production. However, in β-thalassemia major, erythropoiesis-driven suppression of hepcidin often overrides this inflammatory signal (Nemeth et al., 2004), resulting in persistent iron absorption despite chronic inflammation.Genetic mutations also affect hepcidin regulation. Mutations in HAMP, HFE, TMPRSS6 (matriptase-2), or components of the BMP-SMAD pathway can disrupt hepcidin synthesis or signaling (Finberg et al., 2008). Furthermore, epigenetic changes have been shown to suppress hepcidin expression in thalassemia, adding another layer of complexity to iron homeostasis (Muckenthaler et al., 2008).A mutation in the β-globin locus is typically the cause of the β-thalassemia syndromes, which show inadequate or absent β-globin production (Weatherall and Clegg 2001). The production of insoluble aggregates due to the relative excess of α-globin causes inefficient erythropoiesis and limited red cell survival. In addition to variation in other genes, a comparatively high capacity for fetal hemoglobin production is an important genetic modulator of illness severity (Thein 1999). Endocrine and cardiac dysfunction result from increased liver iron and other tissues due to iron overload brought on by enhanced absorption and red cell transfusions (Weatherall and Clegg 2001). Iron can be eliminated and organ function preserved or restored with the help of modern chelation therapies. Red cell survival is shortened and erythropoiesis is unsuccessful in β-thalassemia due to the relative excess of α-globin. Following red cell transfusions, iron excess causes cardiac, endocrine, and hepatic dysfunction (Thein 1999). Deficient (β^{+}) or absent (β^{0}) synthesis of the β-globin component of hemoglobin is a characteristic of β-thalassemia, a hereditary disorder of hemoglobin production (Weatherall and Clegg 2001). Most individuals with thalassemia inherit the condition as a Mendelian



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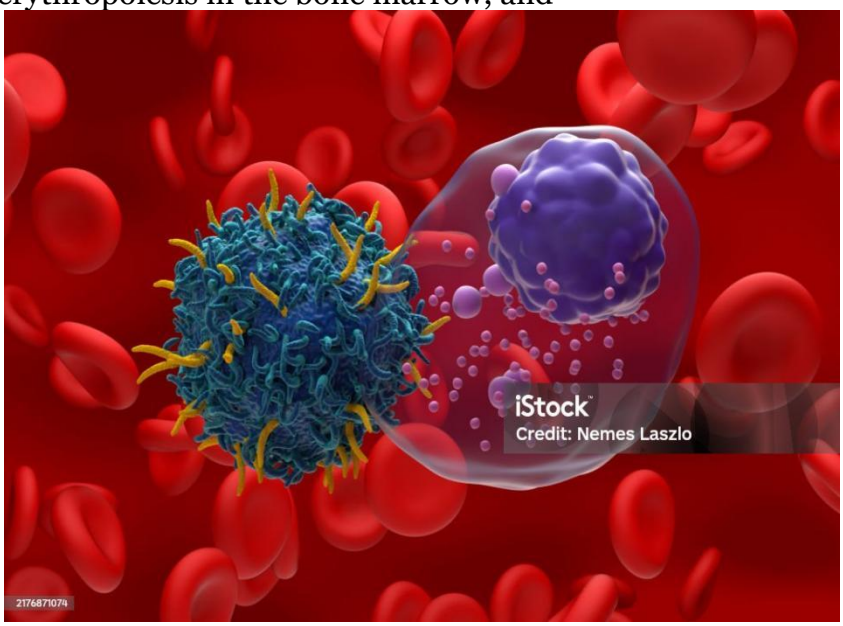
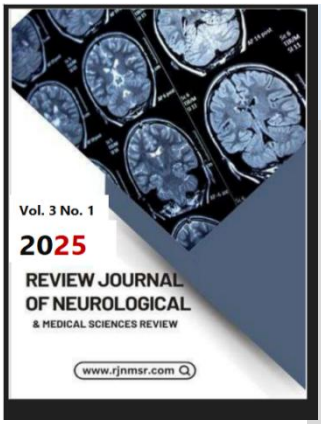
recessive trait. As will be discussed in more detail, homozygous individuals exhibit severe anemia of varying degrees and are classified as having homozygous β-thalassemia (thalassemia major or intermedia), while heterozygous individuals present with mild anemia and microcytosis and are classified as having thalassemia minor (trait) (Thein 1999). Much rarer is dominantly inherited β-thalassemia, which affects heterozygous individuals due to the production of a highly unstable β-globin variant (Thein 1999). Typically, only β-globin synthesis is impaired, though infrequent deletional mutations may eliminate one or more of the beta globin genes (Weatherall and Clegg 2001).The effects of excess, unpaired α-globin are seen in erythropoiesis in people with β-thalassemia. Rather than hemoglobin underproduction, the primary determinant of illness severity is the degree of imbalance in the α-globin to β + γ-globin biosynthesis ratio (Weatherall & Clegg, 2001). The β-thalassemia trait is characterized by a twofold excess in α-globin synthesis, which is consistent with generally normal hematopoiesis accompanied only by minor red cell hypochromia and microcytosis (Thein, 2005). In thalassemia intermedia, the α to non-α biosynthetic ratio is usually *3–4:1, as the effects of excess α-globin production are partially mitigated by residual β-globin synthesis and modest but variable γ-globin synthesis (Rund & Rachmilewitz, 2005). Conversely, **β0-thalassemia* mutations lead to a severe phenotypic manifestation due to a substantial biosynthetic imbalance (Taher et al., 2018). The pathogenesis of β-thalassemia stems from the accumulation of excess free α-globin chains within erythroid cells, resulting from imbalanced synthesis (Weatherall & Clegg, 2001). These chains aggregate, denature, and degrade, forming hemichromes and insoluble precipitates that damage cell membranes (Khandros & Weiss, 2020). Subsequent membrane damage contributes to:

- Hemolysis of circulating red blood cells,
- Ineffective erythropoiesis in the bone marrow, and





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- Splenic red cell loss due to immunoglobulin and complement binding (Nienhuis & Nathan, 2012).

The ensuing anemia triggers reduced tissue oxygenation, elevated erythropoietin levels, and further stimulation of bone marrow expansion, leading to osteopenia and skeletal deformities (Origa, 2017). Additionally, degradation products from damaged red blood cells enhance intestinal iron absorption, resulting in iron overload (Taher et al., 2018).

Hepcidin and Iron Regulation in Health and Disease

Hepcidin, a small peptide hormone released by hepatocytes, circulates in the blood and is excreted in urine (1). It plays a central role in regulating plasma iron levels and systemic iron distribution (2). Dysregulation of hepcidin production is associated with various iron-related disorders: hepcidin excess leads to iron-restricted anemia, while hepcidin deficiency causes iron overload, with iron accumulation in the liver and other tissues (3). Hepcidin exerts its effects by modulating the expression of ferroportin, the only known cellular iron exporter (4). Ferroportin is expressed in:

- Hepatocytes (releasing stored iron),
- Splenic and hepatic macrophages (recycling iron from senescent erythrocytes), and
- Duodenal enterocytes (absorbing dietary iron) (5–7).

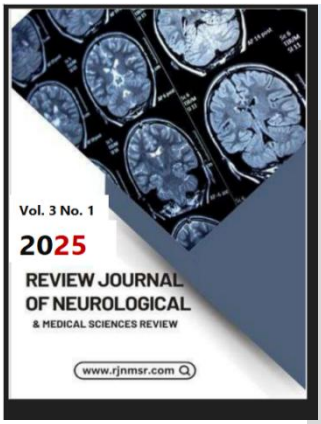
When hepcidin binds to ferroportin, the complex is internalized and degraded, reducing iron export into the plasma (8). Conversely, low hepcidin levels allow ferroportin to remain on the cell surface, increasing iron absorption and release from macrophages. If unregulated, this can lead to systemic iron overload (9).

Regulation of Hepcidin by Iron and Erythropoiesis

Hepcidin production is controlled by iron levels and erythropoietic activity, though this regulation is disrupted in conditions like thalassemia (10). High iron levels (both in plasma and storage) stimulate hepcidin, reducing iron absorption, while iron deficiency suppresses hepcidin, promoting iron uptake (11). The bone morphogenetic protein (BMP) pathway is a key regulator of hepcidin, with BMP6 identified as the primary endogenous activator (12). Mice lacking BMP6 develop severe iron overload (13, 14). Similarly, mutations in hemojuvelin (HJV), a BMP co-receptor, impair hepcidin signaling, leading to iron overload (15). Neogenin, another HJV-interacting protein, also influences hepcidin regulation (16). The HFE and TfR2 proteins sense iron-transferrin levels and modulate hepcidin (17, 18). Increased iron-transferrin enhances HFE/TfR2 interaction, amplifying BMP signaling (19, 20). However, the exact mechanism of intracellular iron sensing remains unclear, as HFE and TfR2 are not strictly required for hepcidin suppression during iron deficiency (21).

Hepcidin in Thalassemia and Iron Overload

In β-thalassemia intermedia, hepcidin levels are suppressed, leading to excessive iron absorption and systemic iron overload (22). The liver, which rapidly takes up non-transferrin-bound iron, is most affected (23). In contrast, transfusion-dependent thalassemia patients have elevated hepcidin due to iron overload and reduced erythropoiesis (24). However, hepcidin levels fluctuate between transfusions, influencing iron absorption (25). Interestingly, iron distribution varies between transfused and non-transfused thalassemia patients: Non-transfused patients



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accumulate iron in hepatocytes, Transfused patients store iron in macrophages (26). This difference affects serum ferritin levels, which may not accurately reflect liver iron content in non-transfused individuals (27). The cellular distribution of iron influences disease progression, as different tissues have varying susceptibility to iron toxicity (28).

Regulation of Hepcidin by Iron and the BMP Pathway

Iron homeostasis and erythropoietic activity regulate hepcidin production, though this mechanism is disrupted in thalassemia (Ganz & Nemeth, 2012). Elevated plasma and stored iron stimulate hepcidin synthesis, inhibiting further iron absorption and preventing iron overload (Nemeth et al., 2004). Conversely, iron deficiency suppresses hepcidin, promoting increased dietary iron absorption and mobilization of stored iron (Ganz, 2011). Both circulating iron-transferrin and intracellular iron stores regulate hepcidin, primarily through the bone morphogenetic protein (BMP) signaling pathway (Meynard et al., 2009). Among BMPs, BMP6 has been identified as the key endogenous regulator of hepcidin (Andriopoulos et al., 2009). While multiple BMPs can induce hepcidin in vitro and in vivo, BMP6 knockout mice develop severe iron overload without other major phenotypic abnormalities (Meynard et al., 2009; Kautz et al., 2008). The BMP co-receptor hemojuvelin (HJV) critically modulates this pathway (Babitt et al., 2006). Mutations in HJV (like those in hepcidin itself) cause severe iron overload in humans and mice, confirming its essential role (Papanikolaou et al., 2004). Similarly, neogenin deficiency in mice results in low hepcidin expression and hepatic iron accumulation, suggesting its involvement in iron-dependent hepcidin regulation (Zhang et al., 2005).

Iron Regulation Mechanism

Hepcidin functions by inhibiting iron absorption in the intestines and the release of iron from stores in the body. Low hepcidin levels lead to increased iron absorption and potential iron overload (Nemeth & Ganz, 2006).

Liver Origin

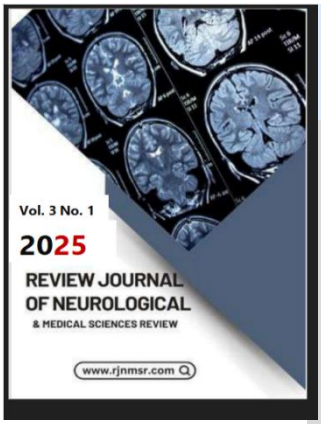
Since the liver is the primary site of hepcidin production, changes in liver function can directly impact hepcidin levels, making it a potential marker for liver damage (Hentze et al., 2010).

Clinical Applications

Hemochromatosis Diagnosis: In patients with hereditary hemochromatosis, low hepcidin levels are often observed due to a genetic defect causing excessive iron absorption, aiding in diagnosis (Beutler et al., 2004).

Liver Disease Monitoring: In patients with chronic liver diseases like hepatitis C or non-alcoholic fatty liver disease, low hepcidin levels can indicate iron overload within the liver, which can worsen liver damage (Hentze et al., 2010).

Transfusion-Related Iron Overload: Monitoring hepcidin levels can be helpful in patients receiving frequent blood transfusions, as low hepcidin may indicate a risk of iron accumulation in organs like the liver (Pippard et al., 1979).



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Limitations to Consider

Inflammatory States: Hepcidin levels can be elevated in inflammatory states, which can complicate interpretation in patients with concurrent inflammation and iron overload (Nemeth & Ganz, 2006).

Not a Standalone Marker: While hepcidin is a valuable indicator, it should be used in conjunction with other clinical parameters like ferritin levels, transferrin saturation, and liver function tests for a complete picture of iron overload and liver damage (Hentze et al., 2010).

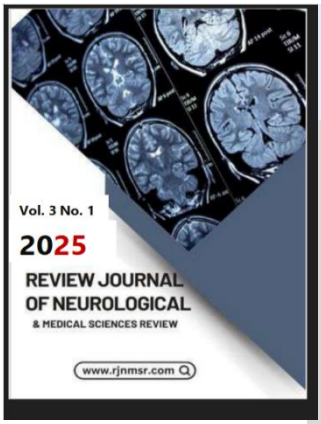
Current Treatment Strategies for Managing Iron Overload in Beta Thalassemia Major

Iron Overload in Beta Thalassemia Major

Iron overload is a major and inevitable complication in patients with beta thalassemia major due to both increased gastrointestinal iron absorption and repeated blood transfusions. Each unit of transfused blood contains approximately 200–250 mg of iron, and since the human body lacks a natural mechanism for excreting excess iron, it accumulates progressively in various organs (Cappellini et al., 2008). Additionally, ineffective erythropoiesis suppresses hepcidin production, which normally regulates iron homeostasis, thereby increasing iron absorption from the gut even when iron stores are already elevated (Kautz et al., 2014). This results in excessive iron deposition in parenchymal tissues such as the liver, heart, and endocrine glands, causing organ dysfunction through oxidative stress and tissue damage (Papanikolaou et al., 2005). Without appropriate iron chelation therapy, iron overload leads to serious complications including liver fibrosis, cardiomyopathy, and endocrine disorders, significantly affecting patient morbidity and mortality.Iron overload in beta thalassemia major occurs due to the accumulation of excess iron from repeated blood transfusions. This excess iron can cause oxidative stress, leading to tissue damage and organ dysfunction. The liver is particularly susceptible to iron overload, which can lead to liver fibrosis, cirrhosis, and hepatocellular carcinoma (Pippard et al., 1979).

Chelation Therapy for Iron Overload

Chelation therapy is the cornerstone of managing iron overload in patients with beta thalassemia major, aiming to prevent organ damage by promoting the excretion of excess iron. Commonly used iron chelators include deferoxamine, deferiprone, and deferasirox, each with different administration routes, efficacy profiles, and side effect spectrums (Cappellini et al., 2006). Deferoxamine, administered parenterally, has been used for decades but often suffers from poor compliance due to its demanding regimen. Oral agents like deferiprone and deferasirox have significantly improved adherence and have shown effectiveness in removing both hepatic and cardiac iron (Porter & Davis, 2002). The choice of chelator and dosing is individualized based on factors such as age, iron burden, organ function, and patient tolerance. Regular monitoring of serum ferritin, liver iron concentration, and cardiac MRI is essential to guide therapy and ensure effective iron removal while minimizing toxicity. Proper chelation significantly improves survival and quality of life in thalassemia patients by reducing iron-induced organ damage (Taher et al.,



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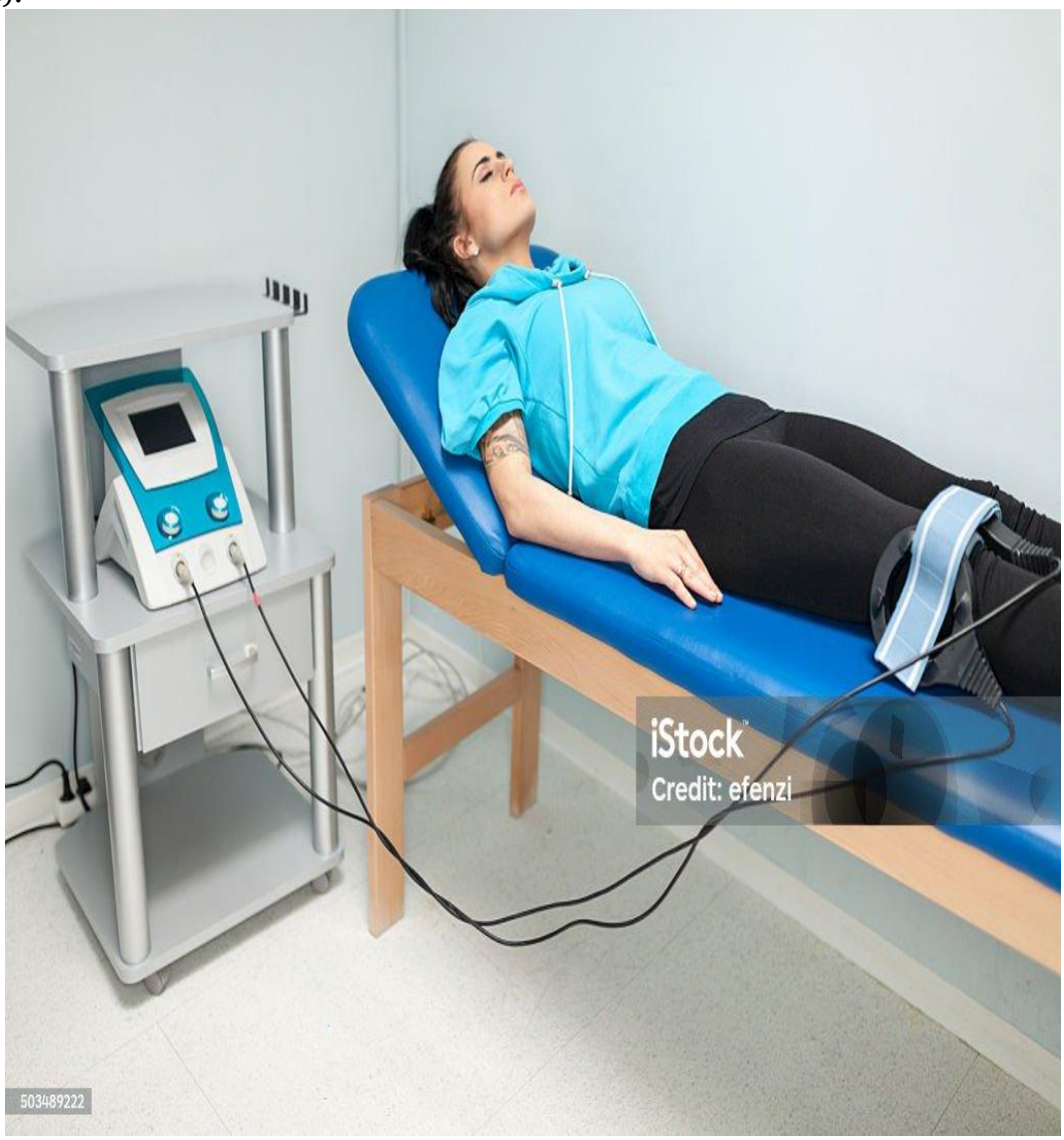
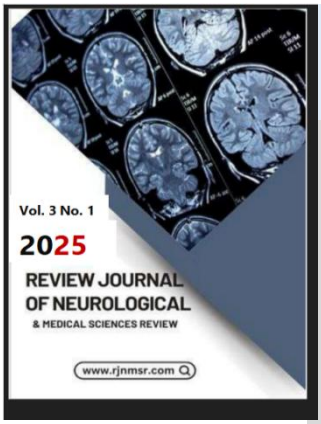
2010).Chelation therapy is the primary treatment strategy for managing iron overload in beta thalassemia major. Chelating agents bind to excess iron, allowing it to be excreted from the body. There are several chelating agents available, including deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX) (Kwiatkowski et al., 2014).



Effects of Chelation Therapy on Hepcidin Levels

Hepcidin is a hormone that regulates iron metabolism by controlling iron absorption and recycling. Chelation therapy can affect hepcidin levels, which can impact iron metabolism. Studies have shown that DFO can increase hepcidin levels, while DFP and DFX can decrease hepcidin levels (Hentze et al., 2010). Chelation therapy not only reduces iron burden in beta thalassemia major but also indirectly influences hepcidin levels by modifying systemic iron homeostasis. As body iron stores decrease with effective chelation, particularly in the liver, the suppression of hepcidin begins



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to reverse, although this response may be variable depending on the extent of erythropoietic activity (Girelli et al., 2011). Some studies have shown that long-term chelation therapy can lead to a gradual normalization of hepcidin levels, particularly when combined with transfusion regimens that limit ineffective erythropoiesis (Pasricha et al., 2013). However, in patients with ongoing high erythropoietic drive, hepcidin may remain inappropriately low despite reduced iron stores, due to persistent overproduction of erythroferrone from the bone marrow (Kautz et al., 2014). Thus, while chelation is effective in managing iron overload, its impact on hepcidin is complex and may not be solely dependent on iron levels, but also on erythropoietic regulation and inflammation.

Effects of Chelation Therapy on Liver Health

Chelation therapy can also impact liver health by reducing iron overload and oxidative stress. Studies have shown that DFO, DFP, and DFX can reduce liver iron concentration and improve liver function (Kwiatkowski et al., 2014). Chelation therapy plays a critical role in preserving liver health in patients with beta thalassemia major by reducing hepatic iron concentration and preventing progressive liver damage. Chronic iron accumulation in the liver, if left untreated, leads to oxidative stress, hepatocellular injury, inflammation, and eventually fibrosis or cirrhosis (Papanikolaou et al., 2005). Effective iron chelation, especially with agents like deferasirox and deferoxamine, has been shown to significantly lower liver iron concentration (LIC) and reduce hepatic enzyme levels, indicating improved liver function (Cappellini et al., 2006). Early and sustained chelation can even reverse mild to moderate liver fibrosis, especially when initiated before the onset of irreversible damage (Angelucci et al., 2000). Regular monitoring of LIC through MRI and liver function tests is essential to tailor chelation regimens and prevent long-term hepatic complications. By controlling liver iron overload, chelation therapy substantially decreases the risk of cirrhosis and hepatocellular carcinoma in these patients.

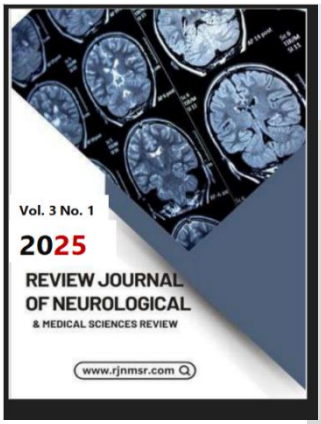
Monitoring and Adherence

Monitoring and adherence are crucial to ensure the effectiveness of chelation therapy. Regular monitoring of iron overload, hepcidin levels, and liver function can help adjust treatment strategies and prevent complications. Adherence to chelation therapy can be improved by patient education, treatment simplification, and support systems (Pippard et al., 1979).

Current Treatment Strategies

Chelation Therapy

Chelation therapy is a medical treatment used to remove excess metal ions from the body by administering chelating agents—compounds that bind to metals and facilitate their excretion, primarily through the urine or feces. In the context of beta thalassemia major, chelation therapy is essential for managing transfusional iron overload, as the human body lacks a physiological mechanism to eliminate excess iron (Porter & Davis, 2002). The most widely used iron chelators include deferoxamine, an injectable agent, and oral agents such as deferiprone and deferasirox, which offer more convenient administration and improved patient



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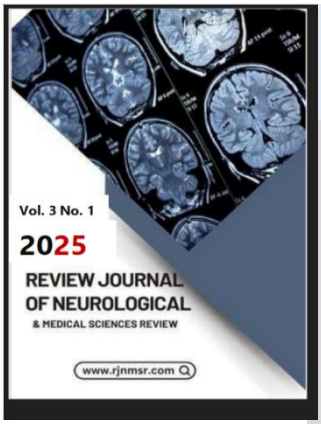
adherence (Cappellini et al., 2006). These chelators form stable complexes with free iron, reducing its availability to catalyze harmful oxidative reactions and preventing iron-mediated damage to vital organs such as the liver, heart, and endocrine glands (Hershko, 1992). Thus, chelation therapy is not only life-prolonging but also essential for improving quality of life and reducing complications in individuals with chronic iron overload.Chelation therapy is the primary treatment strategy for managing iron overload in beta thalassemia major. The goal of chelation therapy is to remove excess iron from the body and prevent organ damage (Kwiatkowski et al., 2014).

Types of Chelating Agents

There are several types of chelating agents available, including:

DFO: Deferoxamine (DFO) is one of the earliest and most established iron chelating agents used in the treatment of transfusional iron overload, particularly in beta thalassemia major. It is a hexadentate chelator that binds iron in a 1:1 ratio, forming a stable complex that is primarily excreted through the urine and bile (Hershko, 1992). Administered via subcutaneous or intravenous infusion, typically over 8–12 hours for 5–7 days a week, DFO has proven efficacy in reducing serum ferritin and liver iron concentration (Olivieri et al., 1994). Despite its effectiveness, its demanding administration schedule often leads to poor compliance, especially in children and adolescents (Porter & Davis, 2002). Long-term DFO use has been associated with a reduced risk of cardiac complications and improved survival, though side effects such as growth retardation, auditory and ocular toxicity may occur, particularly at high doses or in patients with low iron burden (Cappellini et al., 2006). Due to these limitations, DFO is now often used in combination with oral chelators or reserved for patients who cannot tolerate oral therapy.A parenteral chelating agent that has been widely used for decades. It is effective in removing excess iron from the body, but it requires subcutaneous or intravenous administration, which can be inconvenient for patients (Kwiatkowski et al., 2014).

DFP: An oral chelating agent that is effective in removing excess iron from the body. It is often used in combination with DFO to achieve optimal iron removal (Kwiatkowski et al., 2014). Deferiprone (DFP) is an oral iron chelator primarily used for the treatment of transfusional iron overload in patients with beta thalassemia major, particularly those who are unable to tolerate or have inadequate response to deferoxamine (DFO). As a bidentate chelator, DFP binds iron in a 3:1 ligand-to-metal ratio and promotes iron excretion mainly through the urine (Kontoghiorghes et al., 1987). One of the key advantages of DFP is its effectiveness in removing cardiac iron, making it especially valuable in preventing and treating iron-induced cardiomyopathy—a leading cause of death in thalassemia patients (Anderson et al., 2002). Clinical studies have demonstrated that DFP can significantly lower myocardial iron levels and improve left ventricular function, even more effectively than DFO in some cases (Pennell et al., 2006). However, its use requires regular monitoring due to potential side effects such as agranulocytosis, neutropenia, and gastrointestinal discomfort (Cappellini et al., 2006). When used appropriately, either alone or in combination with other chelators, DFP significantly contributes to reducing iron burden and improving clinical outcomes in thalassemia care.



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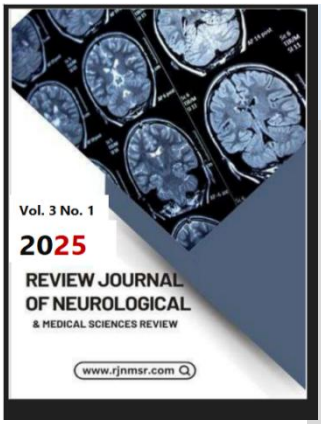
DFX: Deferasirox (DFX) is a once-daily oral iron chelator widely used in the management of chronic iron overload in patients with beta thalassemia major and other transfusion-dependent anemias. It is a tridentate chelator that binds iron in a 2:1 ratio and facilitates its excretion predominantly via the feces (Galanello et al., 2003). DFX offers the convenience of oral administration and long half-life, which improves patient compliance compared to deferoxamine (DFO) (Cappellini et al., 2006). Clinical trials have demonstrated that DFX is effective in reducing serum ferritin levels and liver iron concentration, and it has also shown efficacy in controlling cardiac iron in long-term use (Taher et al., 2009). Common side effects include gastrointestinal disturbances, transient increases in serum creatinine, and, rarely, hepatic or renal dysfunction, requiring regular laboratory monitoring (Cappellini et al., 2006). Due to its favorable efficacy and tolerability profile, DFX is considered a first-line chelator for many thalassemia patients and plays a central role in long-term iron overload management.An oral chelating agent that is effective in removing excess iron from the body. It is often used as a first-line treatment for patients with beta thalassemia major (Kwiatkowski et al., 2014).

Effects of Chelation Therapy on Hepcidin Levels

Chelation therapy has been shown to increase hepcidin levels in patients with beta thalassemia major. Hepcidin is a hormone that regulates iron metabolism, and increased hepcidin levels can help to reduce iron absorption and prevent iron overload (Hentze et al., 2010). Chelation therapy, by reducing body iron burden, indirectly influences the regulation of hepcidin, the key hormone controlling iron homeostasis. In beta thalassemia major, hepcidin levels are typically suppressed due to ineffective erythropoiesis and elevated erythroferrone production, despite significant iron overload (Kautz et al., 2014). Effective chelation therapy—particularly when it significantly reduces liver iron concentration—can help restore the feedback mechanism that regulates hepcidin expression (Girelli et al., 2011). Some studies suggest that with a decrease in hepatic iron and systemic oxidative stress, hepcidin levels gradually increase, although the response can be blunted if ineffective erythropoiesis persists (Pasricha et al., 2013). The modulation of hepcidin through iron chelation not only helps limit further iron absorption from the gut but also may contribute to a more balanced iron distribution and reduced parenchymal damage. However, the relationship between chelation therapy and hepcidin remains complex and is still an area of active research.

Effects of Chelation Therapy on Liver Health

Chelation therapy has been shown to improve liver health in patients with beta thalassemia major. By removing excess iron from the body, chelation therapy can help to prevent liver damage and fibrosis (Kwiatkowski et al., 2014). Chelation therapy significantly improves liver health in patients with beta thalassemia major by reducing hepatic iron overload, a key contributor to liver dysfunction, fibrosis, and cirrhosis. The liver is the primary site of iron storage, and excess iron accumulation leads to oxidative stress, lipid peroxidation, and progressive hepatocellular injury (Papanikolaou et al., 2005). Long-term use of iron chelators such as deferoxamine, deferiprone, and deferasirox has been shown to effectively lower liver iron



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concentration (LIC) and normalize liver enzyme levels, indicating a protective or restorative effect on hepatic function (Angelucci et al., 2000). Deferasirox, in particular, has demonstrated significant efficacy in reducing LIC in both adult and pediatric patients, with once-daily dosing improving compliance and clinical outcomes (Cappellini et al., 2006). Moreover, timely and sustained chelation can prevent progression to liver fibrosis and decrease the risk of hepatocellular carcinoma in chronically transfused patients. Thus, chelation therapy is essential not only for iron control but also for preserving long-term liver health and function.

Monitoring Iron Overload

Serum Ferritin: A blood test to assess iron stores (Pippard et al., 1979).

Liver Iron Concentration (LIC): Measured through liver biopsy, considered the gold standard for assessing liver iron overload (Kwiatkowski et al., 2014).

Cardiac Magnetic Resonance Imaging (MRI): Used to assess myocardial iron deposition (Kwiatkowski et al., 2014).

Monitoring and Adjusting Chelation Therapy

Regular monitoring of iron levels and liver health is essential to ensure that chelation therapy is effective and safe. Adjustments to chelation therapy may be necessary based on individual patient needs (Pippard et al., 1979).Example of Chelation Therapy RegimenHere is an example of a chelation therapy regimen for a patient with beta thalassemia major:

DFO: 40 mg/kg subcutaneously 5 days per week

DFP: 75 mg/kg orally 3 times per day

Future Directions

Development of Newer, More Effective Chelators: Research is ongoing to develop new chelators with improved efficacy and fewer side effects (Kwiatkowski et al., 2014).

Gene Therapy Approaches: Gene therapy holds promise for correcting the underlying genetic defect in beta thalassemia (Pippard et al., 1979).

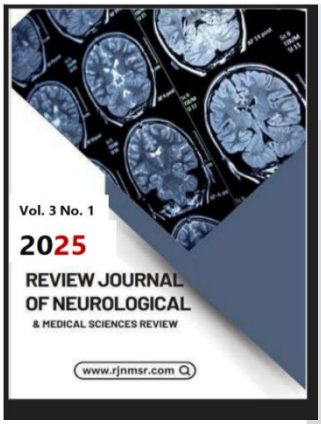
Further Research: Ongoing studies aim to optimize iron chelation strategies based on individual patient needs (Kwiatkowski et al., 2014).

Emerging Therapies for Iron Overload in Beta Thalassemia Major

Beta thalassemia major, also known as Cooley's anemia, is a severe form of thalassemia that requires regular blood transfusions to manage anemia. However, these transfusions can lead to iron overload, which can cause damage to various organs, including the liver, heart, and pancreas (Cunningham et al., 2004). Emerging therapies targeting hepcidin regulation offer potential new treatments for iron overload in beta thalassemia major (Nemeth & Ganz, 2009).

Hepcidin Regulation and Iron Overload

Hepcidin is a key regulator of iron homeostasis, controlling iron absorption and recycling. In beta thalassemia major, hepcidin levels are often decreased, leading to excessive iron absorption and overload (Anderson et al., 2005). Targeting hepcidin regulation offers a promising strategy for managing iron overload (Ganz & Nemeth, 2011).



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Emerging Therapies

Several emerging therapies targeting hepcidin regulation are being investigated for the treatment of iron overload in beta thalassemia major: Hepcidin mimetics are small molecules that mimic hepcidin, binding to ferroportin and reducing iron export (Papanikolaou et al., 2009). Ferroportin inhibitors are small molecules that block the action of ferroportin, reducing iron export and increasing hepcidin levels (Knutson & Oukka, 2008). Hepcidin-inducing agents stimulate the production of hepcidin, leading to reduced iron absorption and overload (Bishop et al., 2013). Gene therapy involves delivering a healthy copy of the hepcidin gene to cells, allowing for the normal production and regulation of hepcidin (Vasavada et al., 2020).These emerging therapies hold promise, but further research is needed to confirm their safety and efficacy in patients with beta thalassemia major (Levy et al., 2015).

Future Directions

Research is ongoing into the development of combination therapies that could integrate emerging treatments with existing chelation therapies (Hershko et al., 2009). Furthermore, the development of personalized medicine based on individual patient characteristics, such as genetic mutations and hepcidin levels, may improve treatment outcomes (Piga et al., 2018). Biomarkers to monitor iron metabolism and hepcidin levels could aid in better diagnosis and treatment monitoring (Kundra et al., 2021).

Hepcidin and Its Regulation

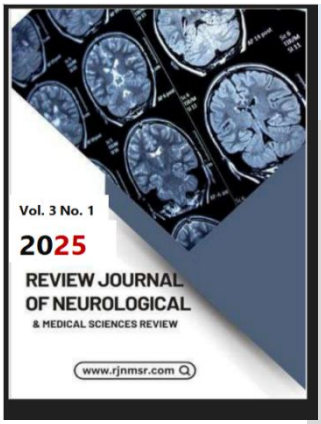
Hepcidin is the key regulator of iron homeostasis in the body, produced mainly in the liver. It controls the amount of iron absorbed from the gastrointestinal tract and the release of stored iron from macrophages (Nemeth et al., 2004). The primary mechanism for hepcidin regulation involves feedback based on iron levels: when iron levels are high, hepcidin levels rise to reduce iron absorption and release. However, inflammation is another major regulator of hepcidin, independent of iron status. Inflammatory cytokines, particularly interleukin-6 (IL-6), stimulate hepcidin production as part of the body's acute-phase response to infection or injury (Weinstein et al., 2002). This response aims to limit the availability of iron to pathogens, which require iron for their growth, but it also results in increased hepcidin levels, which can decrease iron availability for the body's own cells, leading to functional iron deficiency (Fisher et al., 2003).

Inflammation in Beta-Thalassemia Major

Beta-thalassemia major is characterized by ineffective erythropoiesis (abnormal red blood cell production), which leads to chronic anemia (Weatherall & Clegg, 2001). This anemia triggers the body to compensate by increasing iron absorption from the gut and receiving regular blood transfusions. The excess iron from transfusions is not efficiently excreted, resulting in iron overload, which can damage organs (Cunningham et al., 2004).

In these patients, inflammation can arise from a variety of sources:

- The destruction of red blood cells in beta-thalassemia major leads to the release of free hemoglobin, which may trigger inflammatory responses (Gardenghi et al., 2007).



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- Excess iron itself can be a pro-inflammatory agent, leading to oxidative stress and activation of inflammatory pathways (Hershko et al., 2009).
- The frequent transfusions that are needed can also trigger an inflammatory response due to the presence of foreign antigens or immune system activation (Fisher et al., 2003).

Inflammation and Hepcidin Production

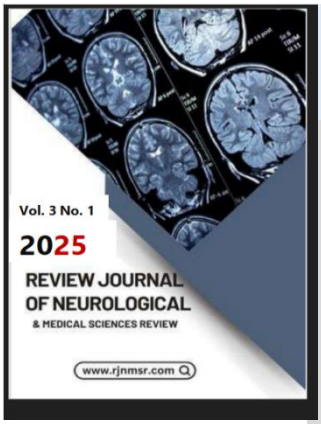
In the presence of inflammation, the liver responds by increasing the production of acute-phase proteins, including hepcidin (Nemeth et al., 2004). This is an attempt to reduce the amount of iron available for pathogens but can have unintended consequences in beta-thalassemia major patients. During periods of inflammation, even if a patient has high iron levels from transfusions, the elevated hepcidin levels may block the release of iron from macrophages (where it is stored) and decrease iron absorption in the gut (Knutson & Oukka, 2008). This can contribute to a functional iron deficiency, where there is plenty of iron in the body, but it is not available for erythropoiesis (red blood cell production) (Thein, 1999).

Impact of Inflammation on Iron Overload Assessment

The assessment of iron overload in beta-thalassemia major is complicated by the influence of inflammation on hepcidin levels. Normally, serum ferritin (a marker of iron stores) is used to assess iron overload, but it is also an acute-phase reactant that increases in response to inflammation (Scherer et al., 2008). Therefore, during inflammatory episodes, ferritin levels can be elevated even if the actual iron load is not increased, potentially leading to false assessments of iron overload. Elevated ferritin levels during inflammation may not accurately reflect the true iron load because both hepcidin-induced iron sequestration and the inflammatory response can artificially raise ferritin levels without an actual increase in iron stores (Anderson et al., 2005). Elevated hepcidin levels in the presence of inflammation inhibit the mobilization of iron from storage sites (such as the liver and macrophages), which may lead to an underestimation of iron overload when relying solely on measures of serum iron (Bishop et al., 2013).

Iron Deficiency vs. Iron Overload

In the context of beta-thalassemia major, where patients are typically transfused with blood to maintain hemoglobin levels, it is important to distinguish between functional iron deficiency (due to high hepcidin levels and inflammation) and iron overload (from transfusions) (Piga et al., 2018). Chronic inflammation can skew the interpretation of iron status, as the body may have adequate iron stores but an impaired ability to utilize them for red blood cell production, leading to functional iron deficiency (Thein, 1999). Thus, measuring hepcidin levels can help in this differentiation. Inflammatory conditions will elevate hepcidin levels, even in the presence of iron overload, indicating that the iron is not being properly utilized (Anderson et al., 2005). On the other hand, if inflammation is not present, hepcidin levels would typically be lower, and iron could be mobilized for erythropoiesis (Gardenghi et al., 2007).



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Managing Iron Overload in the Presence of Inflammation

Given the complexity introduced by inflammation: Managing inflammation through anti-inflammatory therapies (e.g., corticosteroids, IL-6 inhibitors) may help reduce hepcidin production, improving iron mobilization and alleviating functional iron deficiency (Bishop et al., 2013). In patients with persistent iron overload despite inflammation, iron chelation therapy remains essential. This therapy works to reduce excess iron, regardless of inflammatory state, but its effectiveness may be influenced by the presence of elevated hepcidin (Cunningham et al., 2004). In some cases, therapies that target both inflammation and iron chelation may be beneficial (Piga et al., 2018).

Emerging Approaches to Improve Iron Assessment

Hepcidin levels themselves could serve as a useful biomarker in patients with beta-thalassemia major. Lower hepcidin levels would indicate a lack of hepcidin-mediated regulation, and higher levels could suggest that iron is being sequestered due to inflammation, even in the presence of iron overload (Papanikolaou et al., 2009). Combining hepcidin measurements with ferritin and serum iron assessments might offer a more accurate view of iron status in these patients, accounting for both iron overload and the effects of inflammation on iron metabolism (Thein, 1999). In beta-thalassemia major, inflammation plays a central role in modulating hepcidin levels, which in turn affects iron metabolism and the accurate assessment of iron overload (Weatherall & Clegg, 2001). The inflammatory response increases hepcidin levels, causing iron sequestration in storage sites and inhibiting iron absorption, which can lead to functional iron deficiency despite iron overload. This complexity necessitates careful interpretation of iron-related biomarkers, with consideration of the inflammatory state, to properly assess and manage iron overload in these patients (Knutson & Oukka, 2008).

Biological Factors

Inflammation and Infection

Hepcidin is an acute-phase protein and increases during inflammation or infection. Elevated CRP or IL-6 can lead to higher hepcidin levels, falsely suggesting iron sufficiency [1, 2].

Liver Function

Hepcidin is produced in the liver. Liver diseases like cirrhosis or hepatitis can impair hepcidin synthesis, leading to abnormal iron regulation [3].

Erythropoiesis (Red Blood Cell Production)

Increased erythropoiesis (e.g., in thalassemia or after blood loss) suppresses hepcidin, leading to iron overload. Erythroferrone (ERFE), produced by erythroblasts, inhibits hepcidin, confounding the assessment [4, 5].

Genetic Variations

Mutations in HFE (C282Y, H63D), TFR2, or HAMP genes can alter hepcidin expression. Hemochromatosis patients often have inappropriately low hepcidin despite iron overload [6, 7]

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Menstrual and Hormonal Influence

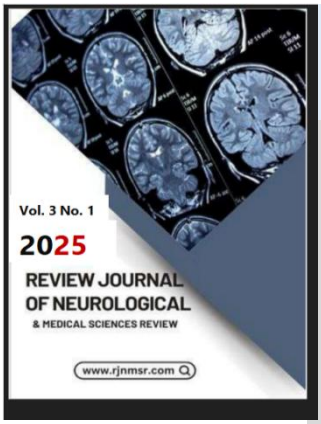
Premenopausal women have lower iron stores due to menstruation, affecting iron markers. Hormonal therapy or pregnancy can also impact iron homeostasis [8].

Methodological Factors

Hepcidin levels follow a diurnal rhythm, peaking in the morning and declining in the evening. Sample collection time must be standardized [9]. Hepcidin levels differ in serum vs. plasma. Improper storage can degrade hepcidin, leading to unreliable results [10]. Different techniques (ELISA, mass spectrometry, or radioimmunoassay) yield variable hepcidin values. Lack of standardization makes inter-study comparisons difficult. Iron supplements, erythropoiesis-stimulating agents (ESAs), anticoagulants, or certain antibiotics may alter hepcidin or iron markers [11, 12].

Clinical and Environmental Factors

High dietary iron (e.g., red meat, supplements) can acutely increase serum iron and affect hepcidin regulation [13]. Polyphenols, phytates, and calcium in the diet inhibit iron absorption, affecting iron markers [14]. Frequent transfusions (e.g., in thalassemia major) introduce iron directly into the bloodstream, overriding normal hepcidin regulation [15]. Chronic kidney disease (CKD) alters iron metabolism and can cause both functional iron deficiency and hepcidin dysregulation [16]. Intense physical activity can transiently alter hepcidin levels. Stress-related hormonal changes (cortisol, adrenaline) may impact iron markers [17].



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Key Takeaways for Research & Clinical Practice

Standardize sample collection time (preferably morning).Measure inflammatory markers (CRP, IL-6) alongside hepcidin to adjust for confounding [18]. Use a consistent assay for hepcidin measurement.Consider genetic screening in patients with unexplained iron overload [19].Account for blood transfusion history in iron overload disorders.

Limitations of Current Research on Hepcidin and Iron Overload Markers

Despite significant progress in understanding hepcidin regulation and iron overload disorders, several limitations exist in current research. These challenges affect the accuracy, applicability, and reproducibility of findings.

Methodological Limitations

Different studies use ELISA, mass spectrometry, or radioimmunoassay, leading to variability in reported hepcidin levels. There is no universally accepted reference range for hepcidin, making inter-study comparisons difficult [20]. Hepcidin exhibits diurnal variation, but many studies do not standardize sample collection times. Sample degradation due to improper storage affects hepcidin and iron biomarker stability [21]. Many studies focus on small cohorts, limiting statistical power. Research is often conducted on specific populations (e.g., Caucasians or specific disease groups like thalassemia patients), making findings less generalizable to diverse ethnic groups [22].

Clinical and Biological Limitations

Hepcidin regulation is affected by multiple physiological and pathological conditions (e.g., chronic kidney disease, infections, pregnancy). Existing models fail to fully capture these dynamic interactions in different disease states [23].

Limited Longitudinal Studies

Most research is cross-sectional, providing only a snapshot of hepcidin and iron markers at a single time point. Long-term studies are needed to assess how hepcidin levels change over time in response to treatment or disease progression [24].

Gaps in Understanding Hepcidin Modulation in Different Diseases

While hepcidin is well studied in hemochromatosis and thalassemia, its role in anemia of chronic disease, cancer, metabolic disorders, and neurodegenerative diseases remains underexplored [25].

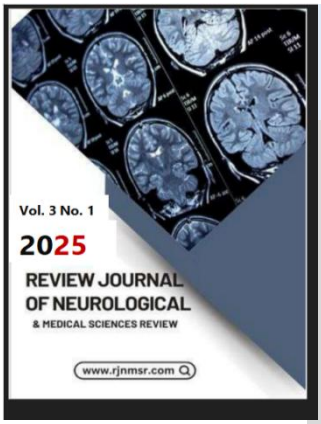
Summary of Key Findings and Clinical Implications for Managing Beta Thalassemia Major Patients

Hepcidin Dysregulation in Beta Thalassemia Major (BTM)

Hepcidin is suppressed in BTM due to chronic erythropoiesis, leading to increased intestinal iron absorption and iron overload. This results in excessive iron deposition in vital organs (liver, heart, pancreas), increasing the risk of complications. Inflammation, infection, genetic mutations (HFE, TFR2, HAMP), and liver dysfunction influence iron regulation [26, 27]. Blood transfusions significantly impact iron levels, making isolated hepcidin measurement less reliable [28].

Limitations of Current Research

Lack of standardized assays for hepcidin measurement affects consistency across studies [29].Small sample sizes and population bias limit generalizability [30].Few



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longitudinal studies assess hepcidin and iron levels over time in BTM patients [31].Current chelation therapy (deferoxamine, deferasirox, deferiprone) is effective but has side effects [32]. Hepcidin agonists (mini-hepcidins, ferroportin inhibitors) show promise in experimental models but require clinical trials [33].Gut microbiome's role in iron absorption remains an underexplored area for future therapeutic interventions [34].

Clinical Implications for Managing Beta Thalassemia Major

Regular monitoring of serum ferritin, liver iron concentration (LIC via MRI), and cardiac iron (T2) is essential [35].Combination chelation therapy (e.g., deferasirox + deferiprone) should be considered in severe iron overload cases [36].Emerging treatments like hepcidin mimetics and ferroportin inhibitors could help regulate iron overload [37].Clinical trials are needed to determine their safety and efficacy in BTM patients [38].Genetic screening for iron metabolism mutations can help tailor iron management strategies [39]. Monitoring inflammatory markers (CRP, IL-6) can aid in better interpreting hepcidin levels [40].MRI-based T2 imaging for cardiac iron should be integrated into routine screening to prevent cardiomyopathy [41].Artificial intelligence (AI) and predictive models could improve risk stratification and early intervention [42].Dietary interventions (low-iron diet, polyphenol-rich foods) may help reduce iron absorption [43]. Exploring gut microbiota manipulation (probiotics, prebiotics, iron chelation through microbiome modulation) is a promising area of future research [44].

Conclusion

Managing beta thalassemia major requires a multidisciplinary approach that includes iron chelation, hepcidin-targeted therapies, non-invasive monitoring, and precision medicine. Future research should focus on standardized hepcidin assays, large-scale longitudinal studies, and novel therapeutics to improve outcomes. By integrating emerging therapies and AI-driven diagnostics, clinicians can enhance the quality of life and long-term prognosis of BTM patients.