Unveiling the Hidden Dangers of Iron Overload – A Systematic Review

Selim Eke (student), Grace Rosner (mentor)

Abstract

Iron deficiency, the leading cause of anemia, has fueled a dramatic rise in the consumption of iron supplements, yet the dangers of iron overload remain largely unrecognized. Iron overload, though less discussed than iron deficiency, can silently wreak havoc on the body, leading to significant organ damage if left unchecked. Excess iron, whether from frequent transfusions, supplements, or genetic conditions like hereditary hemochromatosis, accumulates in vital organs such as the liver, heart, and pancreas. Over time, this build-up can cause irreversible damage, including liver fibrosis, heart failure, and endocrine dysfunction. This review explores the complex pathways through which iron overload affects various organs, highlighting its role in the development of chronic diseases like cirrhosis, cardiomyopathy, and diabetes. As iron excess often goes unnoticed until severe symptoms arise, early detection and targeted treatment strategies are crucial to preventing long-term damage. By understanding the underlying mechanisms and health impacts, this review emphasizes the need for timely intervention in at-risk populations to mitigate the hidden dangers of iron overload.

Keywords

Biomedical and Health Sciences; Cell, Organ, and System Physiology; iron overload; hemosiderosis; ferritin; hepcidin; ferroportin

Introduction

Iron is an essential element known for its critical role in fundamental metabolic processes in the body, including oxygen transport, energy production, and immune response. Iron overload is a condition in which the body absorbs and stores excessive amounts of iron.[1] The primary form of iron overload is a hereditary disorder, known as hemochromatosis. A secondary form known as hemosiderosis may arise from therapeutic interventions such as blood transfusions, along with excessive parenteral or oral administration of iron. The excess iron may accumulate in vital organs like the liver, heart, pancreas, and pituitary gland, potentially causing significant damage if not properly managed. Iron overload can be a serious condition that frequently goes unnoticed due to its vague and slowly progressing nature.

Iron overload may present unseen dangers for human health and may be responsible for morbidity and mortality. While iron deficiency is the most common nutritional cause of anemia in humans, iron ingestion is exponentially increasing around the world, owing to its low cost and availability. Approximately 24.3% of the world's population suffers from anemia, with half of these cases being related to iron deficiency.[2] Disorders of iron excess are much less common than disorders of iron deficiency. Even though less prevalent, the consequences of iron overload are profound. Since humans have no active mechanism to help them eliminate excess iron, the total quantity of iron stored in the body is regulated by the rate of absorption.[3]

Iron overload can be a result of multiple mechanisms, including but not limited to ineffective erythropoiesis, hepcidin suppression, intravenous iron administration, oral iron intake as a supplement or prescription, and red blood cell transfusions for transfusion-dependent anemias

such as thalassemia major. This systematic review aims to explore not only the molecular mechanisms that make iron overload a hidden threat to human health but also its impact on disease progression in the organs that it affects.

Iron is an essential component of myoglobin, heme enzymes, and metalloflavoprotein enzymes. Each hemoglobin molecule contains four iron atoms. Iron is stored in cells in the form of ferritin. Ferritin is a protein-iron storage complex that exists as individual molecules or as aggregates. Serum ferritin is composed of L-chain subunits and is partially glycosylated and increased serum ferritin can be an indicator of iron overload.[4] Aggregated ferritin is referred to as hemosiderin and constitutes a third of normal stores. Essential iron-containing compounds are stored throughout the body, and excess iron is held in the liver for storage. The liver eventually releases iron into the circulation[5]. Iron within the liver is predominantly stored in the reticuloendothelial system, also known as the sinusoidal/Kupffer cells and the hepatocytes. Transferrin is the plasma protein responsible for the internal exchange of iron.[6]

The causes of iron overload can be divided into three main groups: increased intake, increased absorption.

This review delves into the complex mechanisms behind iron overload, exploring its molecular and physiological underpinnings. It examines the role of dysregulated iron homeostasis, including hepcidin suppression, and its impact on conditions such as hereditary hemochromatosis, alcoholic liver disease, and transfusion-dependent anemias. The paper also analyzes how iron-induced oxidative stress contributes to organ damage, including liver fibrosis, heart dysfunction, and endocrine abnormalities. Additionally, it highlights diagnostic challenges, comparing traditional markers like ferritin and transferrin saturation with advanced imaging techniques such as MRI. Finally, this review provides an overview of current therapeutic strategies, including iron chelation and phlebotomy, emphasizing the importance of timely interventions and the need for global improvements in diagnostics and treatment accessibility.

Increased intake

Increased iron intake has multiple causes, including red blood cell transfusions in the management of chronic anemia. In many clinical settings, iron is often prescribed empirically without thorough diagnostic workups, contributing to unintended overload. This is particularly common in cases of hemolytic anemia and myelodysplastic syndromes, where iron homeostasis is disrupted. Additionally, the overuse of iron supplements represents an underrecognized but significant concern, highlighting the need for greater awareness among both healthcare professionals and the public.

Increased absorption

Ineffective erythropoiesis can be seen in certain anemias, in which erythroid precursor cells are unable to properly mature, and are instead apoptosed. This suppresses the release of hepcidin, a hormone inducing intestinal iron absorption. Ineffective erythropoiesis can be encountered in hereditary hemochromatosis, thalassemias, sideroblastic anemia, alcoholic liver disease, and chronic hepatitis. Excessive inhibition of hepcidin by ineffective erythropoiesis explains iron overload in chronic hemolytic anemias. Additionally, hepcidin is reduced in hereditary

hemochromatosis leading to increased iron absorption. Hepcidin suppression leads to upregulation of transport of absorbed iron through the enterocyte basolateral membrane into the systemic circulation.

Patients with alcoholic liver disease have exhibited elevated iron indices and increased body iron stores. Even mild to moderate levels of alcohol consumption have been associated with an increased prevalence of iron overload. Alcohol has been found to induce hepatic oxidative stress alongside iron. Both iron and alcohol are known to inflict cellular damage, leading to hepatocellular injury. However, the definitive underlying mechanisms for excess iron observed in alcoholic liver disease remain unclear.[7] Hepcidin is a hormone responsible for internal iron regulation. There are claims which attribute alcohol to suppress hepcidin synthesis, a hormone responsible for internal iron regulation; the suppression of hepcidin leads to increased iron absorption.

In summary, iron overload can be a result of several factors, including ineffective erythropoiesis, intravenous iron administration, oral iron intake, blood transfusions, and hepcidin suppression. In conditions like major thalassemia and chronic hemolytic disorders, hepcidin, which regulates iron absorption, is suppressed, leading to excessive iron absorption. Elevated levels of hepcidin resulting from chronic inflammation can lead to Anemia of Chronic Disease (ACD) by limiting iron availability for erythropoiesis. In anemic patients, the increased demand for red blood cell production reduces hepcidin production to ensure that more iron is available for hemoglobin synthesis. When the iron-carrying capacity of transferrin is exceeded, iron accumulates as non-transferrin-bound iron (NTBI). Non-transferrin-bound iron can generate reactive oxygen species, inducing toxicity in critical organs such as the liver, heart, pancreas, joints, and pituitary gland. Iron overload poses risks such as liver fibrosis, myocardial damage, bacterial proliferation, and altered gut microbiota. Patients with transfusion-dependent anemias are particularly susceptible, as repeated transfusions introduce large quantities of iron. Erythropoiesis-stimulating agents, like erythropoietin, are able to signal for erythroferrone production, a hepcidin inhibitor which exacerbates the risk of iron-mediated tissue damage and hemosiderosis.[11]

Transfusion-Dependent Anemias

It is known that ferritin and transferrin saturation (TSAT) are elevated in liver disease due to iron release into the bloodstream via senescent hepatocytes. However, there are conditions associated with elevated ferritin levels without iron overload or acute inflammation. An extremely elevated level of ferritin is an indicator of hemophagocytic lymphohistiocytosis.[8]

Transfusional iron overload is another aspect of hemosiderosis. Red blood cell transfusions are used to treat acute and chronic forms of anemia which other treatment options are not available for, such as thalassemia, myelodysplasia and Diamond-Blackfan anemia.[9] Iron overload may occur as a result of frequent red blood cell (RBC) transfusions in major thalassemia, sickle cell disease and thalassemia. The problem arises due to the human body's inability to excrete excess deposits of iron. Although each RBC transfusion is responsible for a subtle amount of iron, it can gradually accumulate and the lack of iron export from the body can lead to iron deposition in several different organs and induce toxicity. Each unit of packed RBC typically contains 200 to 250 mg of elemental iron.[10] As a result, patients with blood transfusion dependent thalassemia inadvertently develop iron overload.

Iron Homeostasis

The regulation of iron homeostasis primarily hinges on the control of dietary iron absorption. Typically, normal plasma levels of iron fall within the range of 12 to 25 µM/L. The iron present in plasma is derived from absorption by enterocytes and macrophages. Ferroportin plays an essential role by exporting iron into the bloodstream. Hepcidin is a protein synthesized in the liver and regulates ferroportin activity. Hepcidin binds to ferroportin to regulate iron homeostasis, a protein which transports iron out of cells; this causes the protein to be internalized and degraded, reducing the amount of iron entering the bloodstream.[12] The process decreases plasma iron concentration. Hepcidin is a negative regulator of intestinal iron absorption as well as macrophage iron release. In an iron deficient condition, such as anemia, hepcidin is down-regulated, while duodenal iron transporters are upregulated, leading to an increase in duodenal iron absorption. During a condition of excess iron, the opposite is true.[13,14] The flow of iron through the plasma amounts to a total of 30 to 40 mg/day in the adult (~0.46 mg/kg of body weight). The major internal circulation of iron involves the erythron and reticuloendothelial cells. About 80% of the iron in plasma goes to the erythroid marrow to be packaged into new erythrocytes, which typically circulate for about 120 days before being catabolized by the reticuloendothelial system.

On the molecular level, hepcidin, the primary regulator of iron export in the body, is a type II acute-phase protein, as suggested by its induction by the cytokine interleukin-6 (IL-6) in a study performed by Nemeth et al. This study demonstrated that iron-sensing cells signal to hepatocytes to induce the production of hepcidin in cases of iron overload. Specifically, the role of hepcidin is to inhibit iron absorption in the small intestine, the release of recycled iron from macrophages, and transport iron across the placenta.[12] Hepcidin circulates in plasma bound to alpha-2-macroglobulin.[15]

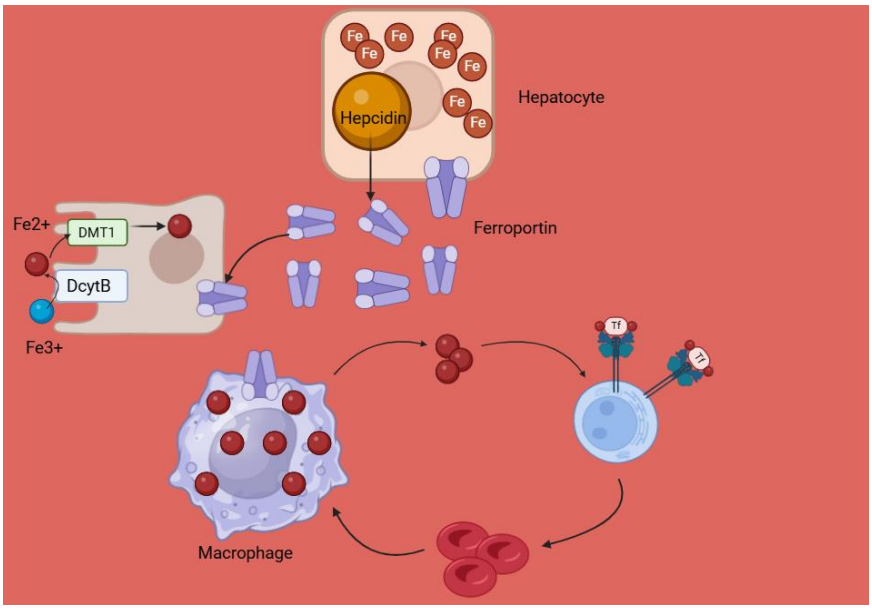

Figure 1. The regulation of iron homeostasis in hemosiderosis

An iron-overloaded hepatocyte is shown. Duodenal cytochrome B (DcytB) reduces Fe(3+) to Fe(2+). Divalent metal transporter 1 (DMT1) at the enterocyte membrane takes up Fe(2+) from the lumen. Transferrin receptor 1 (TFR1) is attached to the erythroblast, saturated by Fe(2+). Hepcidin inhibits ferroportin to mediate iron export to reduce transferrin saturation. In this situation of iron overload, hepcidin is highly expressed.

In cellular absorption, iron transporters transferrin receptor 1 (TFR1) and transferrin receptor 2 (TFR2) are responsible for the internalization of iron. TFR1 can be found in erythroid precursors, the liver, and the myocardium.[16] TFR2, on the other hand, is uniquely found in the liver and intestine.[16] Dietary iron is absorbed by divalent metal transporter 1 (DMT1) before its Fe3+ isotope is reduced to Fe2+ via ferrireductase duodenal cytochrome B (DcytB), as depicted in figure 1 above. Duodenal cytochrome B is encoded by the Cybrd1 gene and is a ferric reductase expressed at the brush border of duodenal enterocytes. Hephaestin is a multicopper oxidase which oxidizes Fe2+ to Fe3+ for loading onto transferrin.[4] However, a study by Gunshin et al. in mice has proved that DcytB is not necessary for dietary iron absorption in mice, but its role in intestinal iron absorption remains unclear.[17] Red cell iron is recycled by macrophages via the protein ferroportin and the ferroxidase ceruloplasmin, which is similar to hephaestin.[4]

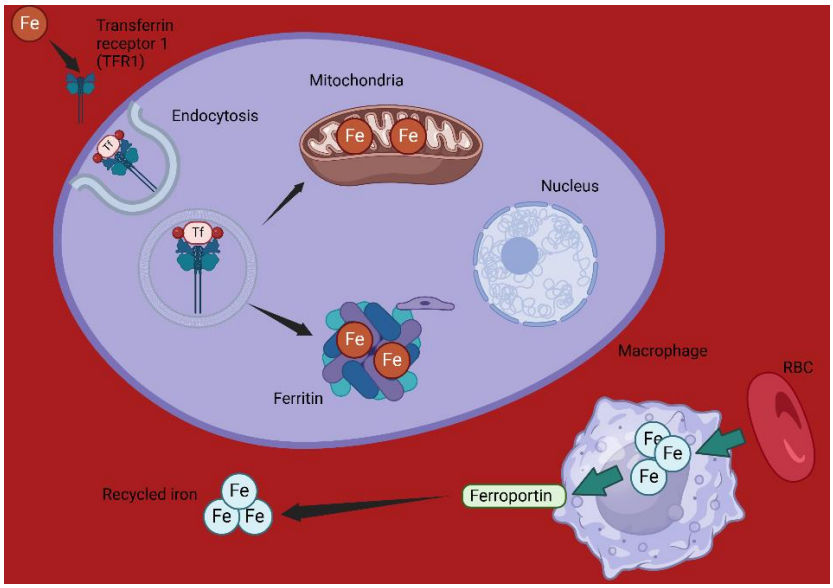

Figure 2. Cellular internalization of iron through TFR1

Before being taken into the cell, iron binds to transferrin receptor 1 and is then endocytosed by the cell. The transferrin-bound iron is then disturbed to organelles, such as mitochondria, and stored in the iron-storage complex, ferritin.

In cases of secondary hemosiderosis, the iron-binding capacity of transferrin in the plasma of iron-overloaded patients is often exceeded, leading to the appearance of non-transferrin-bound iron (NTBI) as shown in Figure 2.[18] During iron overload, reactive oxygen species (ROS) are created which cause oxidative stress.[19] Reactive oxygen species produced by non-transferrin-bound iron can contribute to apoptosis, necrosis, and cellular dysfunction.[16] These reactive oxygen species can also cause tissue damage, inflammation, and fibrosis, especially in organs such as the liver, heart, joints, and pancreas.[20] Freely floating hydroxyl radicals are produced by the Fenton reaction and can damage liver tissue.[21] In contrast, transferrin bound iron is nontoxic.[22]

Past studies have explained the transport of myocardial iron via L-type voltage dependent Ca2+ channels (LVDCCs). Treatment with calcium channel blockers (CCBs) has been shown to prevent deterioration of systolic and diastolic function, as well as bradyarrhythmia, in iron overloaded mice. Treatment with these CCBs also demonstrated a reduction in the composite index of myocardial damage and inflammation and the degree of apoptosis by reducing the potential for myocardial hemosiderosis.[23] This study has major implications for the role of LVDCCs in NTBI accumulation into the myocardium during cases of hemosiderosis.

Moreover, free iron is regarded as being cytotoxic at high concentrations. Elevated ferritin levels related to RBC transfusion have been known to increase risk of acute and chronic graft-versus-host disease (GVHD) in patients receiving hematopoietic cell transplantation. In a mouse model, 10 mg of iron dextran was given to mice over a period of 18 days. Interleukin-1β and interleukin-23 levels were upregulated in iron loaded mice. These findings are believed to explain the mechanism of reduction of regulatory T cells and provides implications for the activation of macrophages in iron overload which could lead to immunological complications, such as GVHD and other autoimmune conditions.[24]

Indications for Iron Administration

Iron deficiency is the most common cause of anemia globally. It is typically diagnosed when ferritin levels fall below 15–30 µg/L and transferrin saturation is less than 20%, often warranting iron supplementation.[25] Populations commonly requiring iron replacement therapy include women of childbearing age, preschool children, patients with end-stage kidney disease, and individuals experiencing gastrointestinal bleeding or malabsorptive conditions. The method of iron replacement must be tailored to the patient's clinical needs, with intravenous or oral administration chosen based on factors such as severity, tolerance, and absorption capacity.[26] In particular, oral ferrous sulfate is frequently the chosen treatment for iron deficiency due to its cost-effectiveness, especially in resource-poor settings. The small intestine regulates absorption, limiting the entry of excessive doses of iron into the bloodstream; it limits absorption to 40 to 60 mg of iron per day in patients with moderately severe iron deficiency anemia. Absorption of iron differs based on type of iron and other factors. Some forms of oral iron have an advantage on absorption. Ferrous salts are absorbed three times as well as ferric salts. Ascorbic acid ≥ 200 mg increases the absorption of medicinal iron by 30%. This increased uptake is associated with a higher incidence of side effects.[6]Once-daily administration of ferrous sulfate 325 mg on an empty stomach is the typical dosage to maximize absorption and simultaneously maintain high tolerance.[27] The iron found in foods is generally insufficient to restore iron levels in someone with iron deficiency. Even iron-rich foods like fortified cereals and organ meats only provide a few milligrams of iron.

There are many conditions where oral iron absorption may be unreliable and parenteral alternatives should be considered. The parenteral route is commonly used for patients with dialysis-dependent chronic kidney disease, malabsorption syndromes, oral iron intolerance, chronic inflammatory conditions, perioperative settings, disorders associated with chronic blood loss and for patients being treated with erythropoietin stimulating agents.[28] As there is no physiological mechanism for excreting excess iron and absorption remains the only regulatory pathway for iron entry into the body, parenteral iron administration poses a heightened risk for iron overload.

High oral iron doses or intravenous iron administration leading to the rapid release of iron may saturate the iron transport system and result in oxidative stress. Once transferrin receptors have been saturated due to excessive intravenous iron administration, significant amounts of non-transferrin bound iron appear and are able to induce toxicity. This NTBI (Fe3+) is readily taken up in an unregulated way by cells of the endocrine system, the heart, and the liver, where it can induce oxidative stress by catalyzing lipid peroxidation and reactive oxygen species formation.[29] Even though iron deficiency is more common, patients who get iron supplements can still end up with iron overload, especially in the setting of predisposition such as undiagnosed thalassemia.

Clinical Impact of Iron Overload on Organ Systems

Excess dietary iron can cause hepatic oxidative stress, inflammation and hepatocellular ballooning, leading to non-alcoholic steatohepatitis (NASH). Kupffer cells full of iron surround dead hepatocytes, inducing inflammation and fibrosis. In cases of chronic hepatitis, iron is known to be a facilitator of liver injury. Patients with high ferritin have more severe steatosis, inflammation, advanced fibrosis, and increased mortality.[19] Alcohol can suppress hepcidin synthesis, a hormone responsible for internal iron regulation; the suppression of hepcidin leads to increased iron absorption.
Iron was proven to exhibit tendencies to cause fibrosis in the liver, dependent on the liver iron concentration (LIC). It has been observed that an increase in hepatocellular injury is reflected in aminotransferase activities when LIC exceeded 300 to 400 µM/g.[30] This study also indicated the ability of iron to induce fibrosis without previous hepatocellular injury in patients being iron overloaded due to blood transfusions for acquired anemias. The quantity of iron in the labile iron pool can be determined based on the urinary iron excretion.

Iron is well known to cause heart dysfunction and failure, hepatic complications, including but not limited to fibrosis, cirrhosis, and hepatocellular carcinoma, along with endocrine disease and growth abnormalities in young children.[31]
Furthermore, iron overload is reported in the pathogenesis of atherosclerosis.[32] NTBI circulates and promotes organ damage like vascular endothelial cell and smooth muscle dysfunction.[33] High labile plasma iron (LPI) and non-transferrin bound iron may increase the risk of myocardial hemosiderosis.[34]
One other aspect of iron overload is pancreatic involvement leading to a clinical picture called bronze diabetes.[35] From an endocrinologic point of view, it is also important to note that MRI of pituitary gland involvement has been reported in individuals with known iron overload but is not routinely used to diagnose iron overload.[36] The classical triad of cirrhosis, diabetes mellitus, and skin pigmentation, so called bronze diabetes, typically occurs when total body iron content is severely elevated, generally over 20 grams.
In a case study for patients receiving allogeneic hematopoietic cell transplantation (HCT), pretransplant serum ferritin levels were measured to determine iron overload. Higher risks of mortality for iron overloaded patients with acute leukemia/myeloid malignancy were exhibited.[37] Elevated ferritin levels were also closely correlated with the development of acute GVHD and blood stream infections for these patients after receiving HCT.
Iron use is associated with potential morbidities. Studies have shown that iron supplementation has resulted in higher rates of malaria, diarrhea, and alterations in the gut microbiome,

increasing susceptibility to enteric pathogens.[38] Iron abundancy is able to cause bacteria to proliferate and form biofilms, making iron overloaded individuals more susceptible to infections.[39] Iron is proven to increase the replication and virulence of enteric pathogens, such as Salmonella, Shigella, and Campylobacter.[40] The impact of iron supplements on diarrhea has been studied in a large metanalysis. 37% of studies showed an increase in overall diarrhea incidence or within a specific subgroup of the population, between iron-supplemented and control groups.[41] Iron supplementation could induce diarrhea by causing intestinal damage through oxidative stress, bacterial dysbiosis and gut inflammation.[42,43]

Diagnosis of Iron Overload

Ferritin is an acute phase reactant, and, along with transferrin and the transferrin receptor, is a member of the protein family that orchestrates cellular defense against oxidative stress and inflammation.[44] A serum ferritin level above 300 ng/mL in males and 150–200 ng/mL in menstruating females may indicate iron overload. In typical cases of iron overload, ferritin levels can range from 2000 to 3000 ng/mL (mcg/L).[45] Raised serum ferritin levels can be due to multiple different etiologies, however, including iron overload, inflammation, liver or renal disease and malignancy.[46] In cases of iron overload, although ferritin is a convenient measure of iron status, it has been demonstrated that its trends are unable to predict changes accurately in LIC in individual patients. Therefore, ferritin trends should be interpreted with caution and confirmed by direct measurement of LIC.[47,48]

A key test for the further investigation of an unexpected raised serum ferritin is the serum transferrin saturation. A TSAT of 45% or higher in males, and 40% or higher in females, often indicates iron overload. Conversely, a TSAT below these thresholds is strong evidence against iron overload, even if ferritin levels are elevated.

Due to its convenience and cost effectiveness, iron levels tend to be monitored by serum ferritin levels and transferrin saturation in clinical practice. The gold standard definitive approach is liver biopsy, but in recent years, non-invasive magnetic resonance imaging (MRI) techniques have been predominantly used to determine compartmentalization of dispersed, ferritin-like iron, and aggregated, hemosiderin-like iron.[49] MRI is used to predict liver iron concentration.[50] Similarly, cardiac involvement can be diagnosed with MRI. A cardiac T2* by MRI <20 milliseconds is indicative of cardiac iron overload.[51]

Nevertheless, there are scenarios in which ferritin and TSAT may not be reliable and can be confounded by other factors as biomarkers for iron overload. Testing for iron should be delayed during times of acute infection and/or inflammation. Furthermore, in a study on patients with sickle cell disease receiving transfusions found that plasma ferritin concentrations did not accurately reflect liver iron levels, reinforcing that ferritin alone is an imprecise marker of iron overload. In this study, quantitative liver iron showed a strong positive correlation with the cumulative months of transfusion ($R = 0.795$, $P < 0.001$), even with the aggressive use of deferoxamine chelation. In contrast, a poor correlation was observed between average serum ferritin and liver iron measured through biopsy ($R = 0.350$, $P = 0.142$).[52]

In a study examining iron overload in dialysis patients, serum ferritin was measured to determine whether or not it was an accurate predictor of iron overload. Seven adults on dialysis

had their serum ferritin values compared to their liver iron values measured via MRI, with the MRI considered to be proportional to the true value of total body iron. The authors deduced that while ferritin may trend downwards, liver iron concentration may remain unchanged. Thus, serum ferritin is an underestimation of LIC in patients undergoing hemodialysis.[53]

Legislation Boosting Intravenous Iron Use

Iron overload is a common complication still encountered in the end-stage kidney disease population due to generous use of intravenous iron, according to current practice patterns. End-stage kidney disease patients suffer from hypoproliferative erythroid marrow function induced by lack of adequate erythropoietin release, accompanying increased iron loss due to procedure of dialysis and other mechanisms. Historically, kidney failure patients suffered from iron overload due to excessive red blood cell transfusions before the invention of human erythropoietin stimulating agents (ESAs). While erythropoietin stimulating agents are widely available, their cost remains elevated and since 2011, bundling changed financial coverage of cost from Medicare/Medicaid to dialysis-providing networks. The challenges around a bundled system's payment constraints are balanced by the move toward value-based care models. This led to the emergence of patient care models for dialysis networks to limit ESA use, while allowing generous administration of intravenous iron based on its low cost.[54] In a retrospective study conducted in 2012, 21 of 115 hemodialysis patients were found to have serum ferritin >1,000 ng/mL, and when these 21 cases were further studied by T2* MRI, 19 of them (90%) were proven to have iron overload in the liver.[55] Rostoker et al., in 2012, conducted a study on 119 hemodialysis patients undergoing treatment with ESA and iron therapy, assessing their LIC using T2* MRI. The results showed mild to severe hepatic iron accumulation in 84% of patients, with 36% exhibiting severe iron overload comparable to that found in hereditary hemochromatosis.[56]

Treatment

The two primary treatment options for iron overload are phlebotomy and iron chelation, both of which serve to remove excess iron from the body. When treating cases of hemosiderosis, iron chelation is the main form of treatment for the removal of excess iron from the bloodstream. Studies have demonstrated that the effect of combination therapy using iron chelators is effective to reduce iron burden.[57] Iron chelation is the only way to treat excess iron accumulation when it coexists with anemia. The three main iron chelators are deferoxamine, deferiprone, and deferasirox. Iron chelation therapy seems to restore iron balance and reduce the risk of mortality.[16] Chelation is a costly treatment option and some patients may not have access to this treatment, even if it is the most effective treatment option. In cases of hemochromatosis, phlebotomy can be used to prevent complications in patients with symptoms or organ damage.[58] Continuous phlebotomy is recommended until the patient's serum ferritin levels are ≤50 ng/mL and their transferrin saturation is <50%.[59]

Discussion

While addressing iron deficiency is a major public health goal, excessive use of iron is the trend affecting a large sector of the general public. The facts summarized in this systematic review underscore the critical importance of understanding the molecular mechanisms and clinical

implications of iron overload, particularly as they pertain to patient health. Iron overload, a condition often overshadowed by the global focus on iron deficiency, presents significant risks that extend across multiple organ systems.

Globally, the increasing access and overuse of iron products has created significant burdens in the field of healthcare, with high rates of morbidity and mortality. Iron toxicity is associated with substantial morbidity and increased mortality, which correlate with the extent of overload.[60,61] Ballas et al. 2001, prospectively collected transfusion data from 247 adult patients with sickle cell anemia and correlated the results with clinical outcomes and laboratory markers of iron overload.[62] Over an 11 year time period, 247 adult patients received 4875 units of RBC transfusions. Patients who were determined to have iron overload suffered a higher incidence of organ failure (71% vs. 19%) and significantly higher mortality (64% vs. 5%). Sanz et al. 2008, evaluated the independent prognostic value of transfusion dependency and iron overload in 2994 patients with myelodysplastic syndrome.[63] This data showed that the development of iron overload was significantly correlated with reduced overall survival. Medical policy creators should work on designing new restrictions to avoid excessive iron use.

Secondary iron overload is a prominent issue in modern-day medicine that cannot be ignored and continues to be easily preventable by raising awareness. In the last several decades, changing healthcare policy worldwide created new patient care practices to increase oral and intravenous iron use while reducing the implementation of costly options.[54]

Patients receiving iron must remain wary of the dangers that come with iron intake and must consider their personal vulnerability to excessive intestinal iron absorption. Caution is key when it comes to iron consumption, especially for those with highest susceptibility due to ineffective erythropoiesis and hepcidin suppression.

This review highlights how hepcidin, the key regulator of iron homeostasis, plays a pivotal role in these processes. Dysregulation of hepcidin, whether through genetic factors such as in hereditary hemochromatosis or secondary to conditions like chronic hemolytic anemias, leads to increased iron absorption and subsequent overload. Iron-induced oxidative stress and lipid peroxidation are major contributors to liver injury, with excessive iron catalyzing the formation of reactive oxygen species that damage hepatocytes. This process is exacerbated in conditions where hepcidin is suppressed, allowing unregulated iron absorption and deposition in the liver. Furthermore, the relationship between iron overload and other organ systems, such as the heart and endocrine glands, adds another layer of complexity to patient management. For instance, myocardial hemosiderosis, resulting from iron accumulation in the heart, can lead to heart failure, while endocrine dysfunctions are common in iron-loaded patients, particularly in those with transfusion-dependent anemias.

The diagnosis and management of iron overload pose significant challenges. While serum ferritin and transferrin saturation are commonly used biomarkers, their reliability can be compromised by factors such as inflammation and liver disease. Serum ferritin, though not fully inaccurate and still able to be used as a general marker of iron overload, may not be the best method for diagnosing hemosiderosis.

In the recent decades, the establishing diagnostic step is magnetic resonance imaging to determine liver iron concentration in order to estimate total body iron, even if the historical gold standard has been liver biopsy. As highlighted in the review, non-invasive imaging techniques like MRI have become invaluable tools for assessing liver iron concentration, offering a more accurate reflection of iron stores compared to traditional serum markers. However, these advanced diagnostic methods are not universally available, particularly in resource-limited settings, underscoring the need for improved global access to these technologies.

Clinically, the management of iron overload requires a delicate balance. The use of iron chelation therapy, particularly in patients with transfusion-dependent conditions, is crucial for preventing the long-term complications associated with iron overload. However, the decision to initiate chelation therapy must be carefully weighed against the potential side effects and the patient's overall clinical condition. Moreover, the review emphasizes the need for regular monitoring of iron levels, particularly in high-risk populations such as those with hereditary hemochromatosis, chronic liver disease, or those receiving frequent blood transfusions.

Conclusion

Iron overload is a complex and multifaceted condition with far-reaching consequences for human health. This systematic review has elucidated the molecular mechanisms underpinning iron overload and its impact on various organ systems. The suppression of hepcidin, a key regulator of iron homeostasis, emerges as a central factor in the pathogenesis of iron overload, leading to increased absorption and deposition of iron in the body. The liver, heart, and endocrine systems are particularly vulnerable to the toxic effects of excess iron, which can result in severe complications, including fibrosis, cirrhosis, heart failure, and endocrine dysfunction.

Given the challenges in diagnosing and managing iron overload, particularly in resource-limited settings, there is a pressing need for greater awareness and improved access to diagnostic tools and treatment options. Regular monitoring and timely intervention are essential to prevent the progression of iron-induced organ damage. Ultimately, this review highlights the importance of a comprehensive and individualized approach to the management of iron overload, taking into account the patient's specific risk factors, clinical condition, and the potential benefits and risks of treatment strategies.

Addressing the challenges of diagnosing and managing iron overload, particularly in resource-constrained settings, requires increased awareness and improved access to both diagnostics and treatments. Regular monitoring and early intervention are key to preventing iron-induced organ damage. A holistic approach to iron overload management, considering the patient's specific risk factors, clinical presentation, and carefully weighing the benefits and risks of various treatment options is crucial to preventing iron overload.

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