Journal of Current Veterinary Research

ISSN: 2636-4026

Journal homepage: http://www.jcvr.journals.ekb.eg

Clinical Pathology

Iron Overload-Induced Hepatotoxicity: An Overview

Nahed Saleh[1], Tamer Allam[1], Hadell Hawary[2] and Nermeen Borai El Borai[3*]

(1)Department of Clinical Pathology, Faculty of Veterinary Medicine, University of Sadat City, Egypt.
(2) Analyst at El-Shefa medical laboratory, El-Giza governorate, Egypt.
(3)Department of Forensic medicine and toxicology, Faculty of veterinary medicine, University of Sadat City, Egypt.

**Corresponding author:* Nermeen.borai@vet.usc.edu.eg *Received: 1/8/2023 Accepted: 11/8/2023*

ABSTRACT

Iron is an important vital micronutrient; nevertheless, iron excess may induce cellular toxicity via mediating reactive oxygen species generation, ensuing in oxidative stress and harm to various organs, including the liver, kidney, heart, and others. Iron overload, also called hemochromatosis, is the most severe manifestation of excessive iron accumulation that can occur despite the body's regulatory processes and results in a systemic buildup of iron in the body leading to many adverse effects. Several factors can contribute in including consuming significant amounts of additional iron, iron loading anaemias, frequent blood transfusions, and some genetic mutations. Liver is particularly at risk of the damaging consequences of iron overload due to the fact it's the primary site for storing iron. However, when the liver's iron storage and anti-oxidant capacity is surpassed, iron overload can result in oxidant-mediated hepatotoxicity. Iron is 'kept safe' in health by a regular balance of iron absorption, transport, storage, and use. Further, efficient regulation of systemic iron homeostasis, along with the effective antioxidant systems, is essential to prevent the harmful effects of excessive ROS generation and oxidative damage. Consequently, a thorough understanding of iron metabolism, mechanisms of iron overload-induced toxicity concomitantly with characterization the optimal methods of assessment and monitoring its adverse effects is crucial for preventing iron-related disorders and for employing successful treatment and control.

Key words: Hepatotoxicity, Iron, Oxidative stress and Reactive oxygen species.

INTRODUCTION

Iron is a key micronutrient and an essential necessity for life, which is commonly involved in critical physiological events which includes transport of oxygen and electron, DNA synthesis, and a variety of enzyme reactions required for basic cellular functions (Pietrangelo 2016 and Wang et al., 2021). Iron is catalytically active element due to its ability to quickly alter valence and transition in-between the ferrous and ferric status, supplying or obtaining electrons, and therefore acting as a mediator in essential biochemical reactions. This chemical characteristic, however, makes iron a major catalyst for the production of dangerous reactive oxygen species (ROS),which result in damage to

lipid, protein, and DNA, resulting in cell death (Dev and Babitt, 2017).

In normal conditions, iron is bound to other molecules such as transferrin, forming the shielded or bound portion of iron in the bloodstream. However, whilst the potential of transferrin to catch iron is handed, iron overload develops (Jenkitkasemwong et al., 2015).

Iron overload or hemochromatosis is identified as systemic buildup of iron in the bloodstream. Iron loading anaemias (congenital dyserythropoietic anaemias, thalassemias, sideroblastic anaemias, myelodysplastic syndromes), Hereditary hemochromatosis, and recurrent blood transfusions are the main causes of systemic iron overload (Imam et al., 2017).

Oxidative stress is a fundamental problem of iron overload and is the main causefor developing worsening health problems over time. Hemochromatosis ends in accumulation of large amounts of free non-transferrin-bound iron (NTBI) (unshielded labile iron) in plasma. NTBI is effortlessly picked up by hepatocytes and other parenchymal cells with iron deposition in these tissues, a condition known as tissue iron siderosis. Inside cells and tissues, iron interferes with redox homeostasis, causing oxidative damage and organ dysfunction (Pietrangelo, 2016; Yang et al., 2018 and Galaris, et al., 2019).

Moreover, iron overload results in various forms of cell death, including cell necrosis, apoptosis, and autophagy (Kruszewski, 2003; Fortes et al. 2012 and Dixon and Stockwell, 2014). At the cellular level, oxidative stress leads to ferroptosis, which is a form of iron-dependent cell death (Galaris et al., 2019). Because the liver is the major organ whose function is to clear excess circulating NTBI in case of iron overload, it is particularly vulnerable to deleterious effects. Iron excess, on the other hand, can cause oxidant-mediated liver injury and hepatotoxicity when the liver's iron storage and antioxidant capacity is exceeded (Dev and Babitt, 2017; Bloomer and Brown, 2019 and Salomao, 2021).

Herein, a comprehensive review on iron metabolism with highlights on the potential detrimental impacts of hemochromatosis, particularly on liver focusing on the underlying mechanisms which may be helpful for monitoring these effects and may offer new opportunities for establishing effective therapeutic strategies. Iron is a chemical element with the symbol Fe (from the Latin ferrum, which means 'iron') and the atomic number 26. It is a metal from the periodic table's first transition series and group 8. Iron is the most prevalent element on Earth by mass, just ahead of oxygen (32.1% and 30.1%, respectively), and the core of the Earth is thought to be entirely made of iron, deposited primarily by meteorites in its metallic condition, with its ores also found there (Anderson and McLaren, 2012 and Lu et al., 2016).

Iron is vital for the functioning of most lifestyles forms and is employed in a diverse array of proteins to fulfill various roles. For instance, iron plays a critical role in heme formation, a crucial prosthetic group in oxygen-binding proteins, such as hemoglobin and myoglobin. Iron is also indispensable for the production of important molecules, which facilitate electron transfer reactions in numerous proteins, including cytochromes, ferredoxins, and dehydrogenases (Duarte, 2020).

1. Iron absorption, uptake, and storage

Dietary iron is the major source for iron supply in the body. Dietary iron has two main forms: heme and nonheme. Iron from animal sources, such as meat and bloodis present as heme-bound iron and is well-absorbed, whereas iron from plant sources, such as grains and vegetables, is present as a

non-heme iron and is not easily absorbed. Both ionic iron (Fe3+) and heme-bound iron are absorbed by enterocytes in the duodenum (Skolmowska and Głąbska, 2019; Milman, 2020 and Ems et al., 2023). Before absorption, ionic iron must be converted to its ferrous state (Fe2+). This reduction is facilitated by cytochrome b reductase (Dcytb) that is present in the brush border of duodenal enterocytes. The reduced ferrous iron (Fe2+) is then transported into enterocytes by divalent metal transporter 1 (DMT1) (Yiannikourides and Latunde-Dada, 2019).

Once inside enterocytes, iron can follow different pathways depending on several factors, including erythropoietic demands, the body's iron stores, and regulatory proteins. It can be stored as ferritin, a protein complex that binds and sequesters iron. This stored ferritin can be later lost when duodenal cells are sloughed off. Iron also can be released into the blood through a protein called ferroportin. On the basolateral side of the duodenum, hephaestin (HEPH) enzyme oxidizes the released Fe2+back Fe3+ to be bound to transferrin (Tf) (Liu and Theil, 2005; Ganz and Nemeth, 2006 and Ems et al., 2023). Certain dietary factors may increase the absorption of non-heme iron. For example, foods rich in vitamin C along with non-heme iron sources can improve iron absorption. Meat, fish, and poultry contain factors that can enhance the absorption of both heme and non-heme iron (Basrowi and Dilantika, 2021 and Consalez et al., 2022).

Conversely, some dietary components can hinder the absorption of iron. Substances like phytates (found in whole grains and legumes), oxalates (found in spinach, beet greens, and rhubarb), and polyphenols (found in tea, coffee, and certain fruits) can bind to iron and form complexes that are less absorbable by the body. Calcium supplements or high-calcium foods, when consumed simultaneously with iron-rich meals, can also lower absorption of iron (Hurrell and Egli, 2010). Iron has the potential to be toxic via generating ROS. To mitigate the potential toxicity of iron, most iron in the body is tightly bound to other molecules for transport and storage purposes (Koskenkorva-Frank et al., 2013 and Aziza et al., 2014).

Iron is delivered in the bloodstream as a compound with transferrin (Tf), a protein that binds iron and enhances its distribution to cells. Bindingof iron-transferrin complex (Fe-Tf complex) to the transferrin receptor, allows distribution of iron to all cells and tissues. Transferrin receptors on the cell surface include transferrin receptor 1 (TfR1) and transferrin receptor 2 (TfR2), via which iron is endocytosed as the Fe-Tf complex. Endocytosis mediated by TfR1 is more efficient than endocytosis mediated by TfR2 (Raje et al., 2007; Td, 2014; Duck and Connor, 2016; Kawabata, 2019 and Ogun and Adeyinka, 2023). The absorbed iron is stored as ferritin primarily in the liver, bone marrow, and spleen, serving as a reserve for future use or it can also be utilized for various functions, such as hemoglobin synthesis in the bone marrow, incorporated into cellular proteins like myoglobin and cytochromes involved in ATP production and electron transport (Knutson, 2017 and Farid et al., 2023).

Within the endosomes, the pH decreases because of the active transport of protons, leading to the dissociation of the Fe-Tf complex. Transferrin and transferrin receptors are then transferred back to the cell membrane, where they can bind iron once more. The extracellular iron in the Fe3+ state after being released from Tf, is then converted by a STEAP family reductase to the Fe2+ state. This Fe2+ iron is transported directly to the cytoplasm via the protein DMT1 contributing to the labile

iron pool within the cell. The labile iron refers to the fraction of iron that is loosely bound and potentially available for cellular processes (Cabantchik et al., 2005; Koren et al., 2010; Cabantchik, 2014 and Coates, 2014).

Iron is primarily stored in the body as ferritin. Ferritin is indeed a globular protein complex composed of 24 subunits that sequesters iron within its core, and its primary function is to store iron intracellularly, primarily within reticuloendothelial cells, hepatocytes, and macrophages. Serum ferritin level is frequently used to estimate the total reserves of iron in the body, with greater serum ferritin levels corresponding to higher iron stores (Arosio and Levi, 2002; Theil, 2012 and Imam et al., 2017).

By sequestering iron, ferritin helps prevent iron toxicity and maintains iron in a safe, non-reactive form within cells preventing it from participating in harmful reactions. This storage capacity allows ferritin to regulate the release of iron in response to cellular iron demands (Bou-Abdallah et al., 2018). Whenever cells' ability to store ferritin is surpassed, iron is deposited within cells in another storage form known as hemosiderin. Which is typically found in cells like macrophages and hepatocytes. Hemosiderin represents aggregates of ferritin that are less accessible for iron release (Puliyel et al., 2015a). Because iron plays a major role in redox signaling and in H2O2-induced toxicity, therefore, even within labile iron pool, iron tends to form complexes with peptides, phosphates, and carboxylates. The binding of iron to these molecules helps to maintain its stability and prevent uncontrolled reactions with ROS (Cabantchik, 2014).

2. Iron homeostasis

To provide adequate iron levels for physiological processes, iron homeostasis is carefully regulated at both the cellular and systemic levels. Key regulatory molecules such as the iron regulatory protein (IRP) system and hypoxia inducible factor (HIF) play critical roles in iron homeostasis within cells (Pantopoulos, 2004; Muckenthaler et al., 2008 and Dev and Babitt, 2017). Systemically, the iron hormone hepcidin is the main regulator of systemic iron homeostasis because it regulates the entry of iron into the circulation from enterocytes, iron recycling macrophages in the reticuloendothelial system, and hepatocytes, thereby controlling iron levels in the body (Hentze et al., 2010; Ganz and Nemeth, 2012 and Bresgen and Eckl, 2015).

Hepcidin exerts its regulatory function by post-translationally repressing the expression of ferroportin which is responsible for exporting iron from cells. When hepcidin levels are high, it causes the internalization of ferroportin, reducing iron export and increasing iron sequestration within cells. Hepcidin can also down regulate the expression of TfR1 and DMT1, further limiting iron export (Drakesmith and Prentice, 2012; Eid et al., 2017and Daher et al., 2017). Hepcidin expression is also closely managed at the transcriptional level via numerous variables including iron concentrations, erythropoiesis, inflammation, and hypoxia. In hepcidin regulation, signaling pathways such as bone morphogenetic protein/suppressor of mothers in opposition to decapentaplegic (BMP/SMAD) and Janus kinase/sign transducer and activator of transcription (JAK/STAT) are involved (Wrighting and Andrews, 2006; Pietrangelo et al., 2007; Core et al., 2014 and Silvestri et al., 2019). As a result, hepcidin production was observed to rise in conditions associated with iron excess and inflammation and reduced in iron deficiency (Suchdev et al., 2017).

3. Biological role of iron

Numerous crucial biological processes are carried out by iron in living beings. Because iron is necessary for hemoglobin production, the protein in red blood cells responsible for delivering oxygen from the lungs to the body's tissues, it is primarily involved in oxygen transport from the lungs to tissues. Hemoglobin and myoglobin contain around 70% of the iron in the body (Zhang, 2014).

Myoglobin is a protein that is only present in muscles and is utilized to store oxygen by binding iron within a heme group. It is structurally similar to hemoglobin, however it is more simpler, having onlyone polypeptide chain of 154 amino acids (Coates, 2014). Furthermore, numerous enzymes need iron as a cofactor to function. Among them, the enzymes involved in oxidative phosphorylation, and themetabolic pathways that transforms nutrients to energy. Iron-sulfur centers are necessary for the operation of some protein complexes in the oxidative phosphorylation pathway. During cellular respiration, iron-containing cytochromes transfer electrons to generate energy in the form of ATP (Mendel et al., 2007 and Pain and Dancis, 2016).

Iron-containing enzymes, such as peroxidase and catalase, participate in antioxidant defense systems, breaking down harmful hydrogen peroxide and protecting cells from oxidative damage. Iron is also required for the activity of ribonucleotide reductase, an enzyme essential for the production of deoxyribonucleotides, which are essential for DNA synthesis and repair (Góth et al., 2004 and Kumral et al., 2005). Further, iron is necessary for the synthesis of neurotransmitters, including dopamine and serotonin, which play critical roles in communication ofnerve cells. Iron is necessary for the immune system to operate properly because it promotes immune cell proliferation and maturation. Therefore, iron provides a crucial role in the defense against microbial pathogens(Oni and Nyokong, 2000 and Ganz, 2009).

4. Iron overload-induced toxicity

Although iron is necessary for various cellular processes, increased iron leads to iron accumulation or iron overload, which is toxic via triggering the production of free radicals (Wang and Babitt, 2019). Iron overloadis the most severe form of excessive iron accumulation that can occur despite the body's regulatory mechanisms and resulting in a systemic iron buildup in the body. The adverse effects of iron overload become apparent when the available binding sites for iron, such as transferrin proteins, become saturated (Imam et al., 2017).

Since the body has no excretory mechanisms for iron andany excess iron cannot be easily excreted , high saturation levels of serum transferrin leads to accumulation of significant amounts of free NTBI also called unshielded labile iron in plasma (Brissot et al., 2012; Fleming and Ponka, 2012 and Jenkitkasemwong et al., 2015). Unshielded labile iron accumulated in plasma is easily picked up by hepatocytes and different parenchymal cells througha NTBI transporter called ZIP14, resulting in iron deposition in those cells and thus tissue damage contributing to the development of various diseases (Jenkitkasemwong et al., 2015).

Hemochromatosis can be either genetic or acquired. Hereditary hemochromatosis (HH) is a genetic disorder brought in a mutation in the hemochromatosis gene (HFE) that results in excessive buildup of iron in the body. Moreover, mutations in genes such as hemojuvelin (HJV) and hepcidin antimicrobial peptide (HAMP) are linked to HH, particularly in cases of juvenile hemochromatosis. These mutations disrupt iron absorption and result in increased iron levels in the plasma with subsequent

increase in NTBI (Camaschella et al., 2000; Åsberg, 2001; Silva and Faustino, 2015b and Yun and Vincelette, 2015).

In addition to primary hereditary hemochromatosis (HHC), several conditions can also contribute to increased iron levels in plasma, resulting in iron toxicity. These conditions include secondary hereditary and acquired hemochromatosis, which is usually observed with excessive oral iron ingestion, transfusional iron overload, and hyperferritinemia (Coates, 2014 and Meloni et al., 2014). The storage of iron as ferritin and hemosiderin inside cells seems to function as a protective mechanism towards the toxic effects of NTBI and the stored iron does no longer show immediate toxicity. However, if left untreated over a prolonged period, excessive levels of both extracellular and intracellular iron can give rise to serious pathological consequences of iron-related toxicity (Cabantchik et al., 2005).

5. Adverse effects of iron overload

Iron overload can have adverse effects on various organs. Excess iron may induce liver fibrosis, cirrhosis, and hepatocellular carcinoma. Heart can be severely affected with iron overload resulting in cardiomyopathy, which is characterized by functional and structural abnormalities of the heart muscle with an increased risk of heart failure (Fishbaneet al., 2014 and Bloomer and Brown, 2019). Other adverse effects of iron overload include pancreatic dysfunction with a higher risk of developing diabetes mellitus, disruption of hormone production and regulation, resulting in endocrine disorders, excessive iron deposition in the joints (hemosiderotic arthropathy) which can lead to joint pain, inflammation, and arthritis in addition to skin pigmentation changes, resulting in a bronze or grayish discoloration known as bronze diabetes or hemochromatotic pigmentation, the most commonly observed in individuals with hereditary hemochromatosis (Singer et al., 2020; Yang et al., 2020 and Sha et al., 2021).

The severity of iron overload on different organs can vary among individuals in relation to many factors such as the underlying cause of iron overload, duration, and extent of iron buildup, and individual susceptibility. Iron overload disorders must be diagnosed and managed as soon as possible to prevent or reduce the negative impacts on organ function and overall health (Shander et al., 2009).

6. Iron overload-induced hepatotoxicity

The liver is particularly vulnerable to the harmful effects of iron overload. Iron overload can lead to hepatotoxicity, which refers to damage of hepatocytes because of excessive iron build up in the liver. Iron overload promotes ROS production leading to damage of liver cells and contribute to inflammation and tissue injury. Prolonged iron overload can cause chronic inflammation and scarring of the liver, resulting in fibrosis and eventually cirrhosis. Cirrhosis can disrupt liver function and impair its ability to perform essential tasks (Salomao, 2021). Furthermore, long-term iron overload, especially when combined with underlying liver disease such as cirrhosis, can increase the chance of developing the most prevalent kind of liver cancer the hepatocellular carcinoma (Paganoni et al., 2021). However, the severity and progression of hepatotoxicity in iron overload can vary among individuals and depend on various factors, including the underlying cause of iron overload, duration of iron accumulation, and presence of other liver diseases. Early detection, diagnosis, and monitoring of iron overload are crucial in preventing or minimizing hepatotoxicity (Bloomer and Brown, 2019).

7. Mechanisms underlying iron overload-induced hepatotoxicity

i. Oxidative stress

Oxidative stress is a fundamental problem of iron overload and is a major reason for developing worsening health concerns over time. ROS, including free radicals, are created as byproducts of regular metabolic activities in the body. However, the body has evolved detoxification systems to control the formation of ROS and mitigate their negative consequences. Otherwise, oxidative stress develops. The imbalance between ROS and intracellular antioxidants is the main cause of cellular oxidative stress (Valko et al. 2007). The ability of iron to easily change its valence and transition between the Fe2+ and Fe3+ forms, supplying or accepting electrons, makes it the primary catalyst for the creation of ROS in aerobic organisms. In pathologic conditions that result in iron overload, there is an increased amount of unshielded redox-active iron which favors Fenton reaction yielding extremely reactive hydroxyl radical ($OH^{\cdot}$) (Kitsati, 2016; Pietrangelo, 2016 and Galaris et al., 2019).

Hydroxyl radicals are very reactive and can harm biological components by peroxidizing polyunsaturated phospholipids in organelle and cellular membranes, oxidizing amino acid side chains, breaking DNA strands, and fragmenting proteins. These processes contribute to cellular and tissue damage associated with conditions of iron overload and oxidative stress (Bresgen and Eckl, 2015 and Yang et al., 2018). Lipid peroxidation is a consequence of cellular oxidative stress which results from oxidative lipids degradation, particularly unsaturated fatty acids, by ROS. During lipid peroxidation, peroxyl radicals ($ROO^{\cdot}$) are formed which are highly reactive and can initiate further lipid peroxidation reactions (Galaris et al., 2019).

ii. Cell Death

Iron overload is closely-linked to several types of cell death, including necrosis, apoptosis, and autophagy (Kruszewski, 2003; Fortes et al. 2012; and Dixon and Stockwell, 2014). Another form of iron-dependent cell death is ferroptosis was recently discovered. The link between ferroptosis and systemic iron metabolism is complicated, but it bears potential as a therapeutic goal in iron overload circumstances (Jiang et al., 2015 and Galaris et al., 2019).

Ferroptosis varies from other types of cell death, in terms of morphology, biochemistry, and genetics. It is characterized by increased intracellular labile iron, lipid peroxidation at the plasma membrane, which causes damage to inner membrane phospholipids, particularly cardiolipin, and a deficiency of decreased nicotinamide adenine dinucleotide phosphate (NADPH) (Dixon et al., 2012 and Garcia-Perez et al., 2013).This may be followed by an increase in lysosome vulnerability, a decline in cytochrome activity and mitochondrial damage, which is the main targets of iron toxicity (Ramm and Richard, 2005; Fortes et al., 2012 and Philpott and Ryu, 2014). Furthermore, the iron-containing molecule heme promotes necrosis in macrophages whereas heme increases the expression tumor necrosis factor (TNF) which in turn stimulates other signaling pathways resulting in cell necrosis (Lu et al., 2016).

8. Clinicopathological monitoring of iron overload-induced toxicity

Monitoring iron overload is critical for identifying existing problems, assessing the risk of future complications, and hence preventing or minimizing the future complications from arising (Shah et al., 2022). Further, the identification and monitoring of iron overload is a critical component in the development of improved iron chelation therapy procedures that may

be tailored to the patient's particular needs. However, there are some standards for monitoring iron overload that can be applied to all regimes (Taher et al., 2009).

i. Serum ferritin

Serum ferritin is a laboratory test that measures the level of ferritin. Iron is primarily stored in ferritin that is readily available for use and also helps prevent iron toxicity and maintains iron in a safe, non-reactive form within cells. Ferritin is mainly found intracellularly but because it is water soluble it can be detected in serum as an indicator of iron stores in the body (Adams, 2008 and Jung et al., 2013). Serum ferritin is crucial in evaluating the overall risk of iron overload problems and is especially helpful for long-term trends. Typically, serum levels of ferritin are directly-linked to the body's iron stores, with higher levels indicating increased iron stores and can suggest iron overload while, lower levels suggesting depleted iron stores and are indicative of iron deficiency (Shah et al., 2022).

Although ferritin levels in the serum are usually considered as an indicator of the total body iron stores, with higher serum ferritin levels corresponding to higher iron stores. However, it is important to note that ferritin as it is an acute-phase protein therefore, pathological conditions unrelated to iron status, such as tissue damage and inflammation can also increase serum ferritin levels (Wang et al., 2010 and Imam et al., 2017).

ii. Saturation percent of transferrin

Saturation percent of transferrin (Tf sat%) is a laboratory test that measures the percentage of transferrin that is saturated with iron. It provides information about the portion of serum iron that is bound to transferrin in the blood and can reflect the body's iron status (Anderson and McLaren, 2012 and Elsayed et al., 2016).

Low Tf sat% values (typically less than 16-20%) indicate reduced iron availability for binding to transferrin, which is commonly seen in iron deficiency anemia. Conversely, high Tf sat% alues (greater than 45-50%) may suggest increased iron absorption or excessive iron stores, which can be seen in conditions of iron overload such as hereditary hemochromatosis or chronic transfusion therapy (Shah et al., 2022).

iii. Labile plasma iron

Measuring LPI levels can provide valuable information about the labile or reactive iron fraction in the plasma.LPI is considered to be a potentially toxic form of iron because it can participate in redox reactions, generating ROS that can cause cellular damage and thus the levels of LPI may increase in pathological conditions, associated with iron overload leading to oxidative stress (Koren et al., 2010; Kitsati, 2016 and Galaris et al., 2019).

iv. Quantification Liver iron (Liver iron concentration)

Liver iron quantification, commonly known as liver iron concentration (LIC) measurement, is a technique for determining the quantity of iron stored in the liver. It is a critical diagnostic technique for assessing iron overload disorders such as hereditary hemochromatosis, transfusional iron overload, and other conditions that result in excessive hepatic iron accumulation (Anderson and McLaren, 2012). Data from LIC measurements taken from biopsies have demonstrated that long-term LICs greater than 7 mg/g

dry weight have been linked to a greater occurrence of fibrosis (Shah et al., 2022).

v. Markers of oxidative damage

Markers of oxidative damage are detectable variables that indicate the existence of oxidative stress (Sies et al., 2017). Common oxidative damage indicators include lipid peroxidation products such as Malondialdehyde (MDA) (Su et al., 2019) and 4-hydroxynonenal (4-HNE) (Zhong and Yin, 2015) which are often measured as indicators of oxidative damage to cell membranes. Protein carbonyls are widely used as markers of protein oxidation and are quantified as a measure of oxidative damage to cellular proteins (Dalle-Donne et al., 2003). 8-hydroxy-2'-deoxyguanosine (8-OHdG) is one of the most frequently measured biomarkers of oxidative damage to DNA caused by ROS (Urbaniak et al., 2020). Additionally, advanced oxidation protein products (AOPPs) are complexes formed by the interaction of ROS with plasma proteins. They are considered markers of oxidative protein damage and are associated with various inflammatory and chronic diseases (Krzystek-Korpacka et al., 2008).

9. Management and treatment of iron overload- induced hepatotoxicity

To manage iron overload and mitigate the associated side effects, surplus iron load should be cleared away from body to keep iron at its safe natural levels and thus minimize the toxic effect of iron overload that helps protect organs from iron-related damage (Coates et al., 2016; Imam et al., 2017 and Entezari et al., 2022). Iron chelation therapy has recently gained greater interest in medicine, with promising outcomes for the management of iron overload. The main goal of chelation therapy is to eliminate extra iron and prevent its accumulation, hence lowering the risk of and problems associated with iron overload (Mobarra et al., 2016 and Carver, 2019).

Deferoxamine and deferasirox, iron chelators, are currently available for the treatment of iron overload in various clinical conditions and each have their own benefits and drawbacks (Mobarra et al., 2016 and Entezari et al., 2022). Deferoxamine (Desferal) is the oldest and most established iron chelator. Deferoxamine is administered primarily through subcutaneous or intravenous infusions and thus is often used in cases of acute iron overload and in individuals who cannot tolerate oral chelators (Aalikhani et al., 2022). Deferasirox (Exjadeor Jadenu) are oral chelating agents that can be taken once daily. They offer more convenience for long-term treatment, and their effectiveness is comparable to deferoxamine (Oyedeji et al., 2021). Deferiprone (Ferriprox) is another oral chelator for the treatment of iron overload, particularly in patients with thalassemia (Chaudhary et al., 2021).

Recently, Plant-based drugs have grown as complementary and alternative treatments, resulting in the creation of a diverse range of biologically active compounds that exert their effects via interactions with biological pathways (Hassanzadeh, 2014). Many of these compounds were proven to have iron chelating and antioxidant activities, allowing them to play an essential role in management of iron overload and are predicted to be developed as natural supplementary medicines for the

management of iron homeostasis disorders (Darvishi-Khezri et al., 2016; Volkova et al., 2020 and Wang et al., 2021).

CONCLUSIONS AND FUTURE PROSPECTS

While iron is required for many biological functions, excess iron can be hazardous to cells due to its participation in the generation ROS, which needs strict regulation to avoid uncontrolled interactions with ROS and the subsequent cellular damage. Hence, the conclusion can be made that a thorough understanding of iron metabolism and mechanisms underlying iron overload-toxicity with optimal iron overload assessment and monitoring is essential for detecting the existing problems, quantifying the risk of, and therefore preventing iron-related disorders. Such data is also helpful in the development of successful strategies for the treatment and control.

REFERENCES

Aalikhani, M.; Safdari, Y.; Jahanshahi, M.; Alikhani, M. and Khalili, M. (2022): Comparison Between Hesperidin, Coumarin, and Deferoxamine Iron Chelation and Antioxidant Activity Against Excessive Iron in the Iron Overloaded Mice. Frontiers in Neuroscience, 15: 811080. https://doi.org/10.3389/fnins.2021.811080.

Adams, P. (2008): Management of elevated serum ferritin levels. Gastroenterology & Hepatology, 4(5):333–334.

Anderson, G. J. and McLaren, G. D. (2012 Iron Physiology and Pathophysiology in Humans. Humana Press. Part of the book series: Nutrition and Health (NH). https://doi.org/10.1007/978-1-60327-485-2.

Arosio, P. and Levi, S. (2002): Ferritin, iron homeostasis, and oxidative damage. Free Radical Biology and Medicine, *33*(4): 457–463. https://doi.org/10.1016/S0891-5849(02)00842-0.

Åsberg, A. K. H.; Thorstensen, K.; Ellekjaer, E.; Kannelønning, K.; Fjøsne, U.; Halvorsen, T. B.et al. (2001): Screening for Hemochromatosis: High Prevalence and Low Morbidity in an Unselected Population of 65,238 Persons. Scandinavian Journal of Gastroenterology, *36*(10): 1108–1115. https://doi.org/10.1080/00365520175 0422747.

Aziza, S. A. H.; Azab, M. E. S. and El-Shall, S. K. (2014): Ameliorating role of rutin on oxidative stress induced by iron overload in hepatic tissue of rats. Pakistan Journal of Biological Sciences, 17(8): 964–977. https://doi.org/10.3923/pjbs.2014.964.977.

Basrowi, R.B. W. and Dilantika, C. (2021): Optimizing iron adequacy and absorption to prevent iron deficiency anemia: The role of combination of fortified iron and vitamin C. World Nutrition Journal, 5(1–1): 33–39. https://doi.org/10.25220/WNJ.V05.S1.0005.

Bloomer, S. A. and Brown, K. E. (2019): Iron-Induced Liver Injury: A Critical Reappraisal. International Journal of Molecular Sciences, 20(9): 2132. https://doi.org/10.3390/ijms20092132.

Bou-Abdallah, F.; Paliakkara, J. J.; Melman, G. and Melman, A. (2018): Reductive Mobilization of Iron from Intact Ferritin: Mechanisms and Physiological Implication. Pharmaceuticals, 11(4): 120. https://doi.org/10.3390/ph11040120.

Bresgen, N. and Eckl, P. M. (2015): Oxidative Stress and the Homeodynamics of Iron Metabolism. Biomolecules, 5(2): Article 2. https://doi.org/10.3390/biom5020808.

Brissot, P.; Ropert, M.; Le Lan, C. and Loréal, O. (2012): Non-transferrin bound iron: A key role in iron overload and iron toxicity. Biochimica et Biophysica Acta (BBA) - General Subjects, 1820(3): 403–410. https://doi.org/10.1016/j.bbagen.2011.07.014.

Cabantchik, Z. I. (2014): Labile iron in cells and body fluids: Physiology, pathology, and pharmacology. Frontiers in Pharmacology, *5*. https://doi.org/10.3389/fphar.2014.00045.

Cabantchik, Z. I.; Breuer, W.; Zanninelli, G. and Cianciulli, P. (2005): LPI-labile plasma iron in iron overload. Best Practice & Research Clinical Haematology, 18(2): 277–287. https://doi.org/10.1016/j.beha.2004.10.003.

Camaschella, C.; Roetto, A.; Calì, A.; De Gobbi, M.; Garozzo, G.; Carella, M. et al (2000):The gene TFR2 is mutated in a new type of haemochromatosis mapping to 7q22. Nature Genetics, *25*(1):Article 1. https://doi.org/10.1038/75534.

Carver, P. L. (2019): Essential Metals in Medicine: Therapeutic Use and Toxicity of Metal Ionsin the Clinic. Walter de Gruyter GmbH & Co KG.

Chaudhary, J. L.; Rathi, S. G.; Shah, S.; Patel, J. T. and Vaghela, S. (2021): Deferiprone (Ferriprox) as newer iron chelator in thalassemia major patients. Research Journal of Pharmacy and Technology, 14(2): 1041–1044. https://doi.org/10.5958/0974-360X.2021.00186.4.

Coates, T. D. (2014): Physiology and pathophysiology of iron in hemoglobin-associated diseases. Free Radical Biology and Medicine, 72: 23–40. https://doi.org/10.1016/j.freeradbiomed.2014.03.039.

Coates, T. D.; Carson, S.; Wood, J. C. and Berdoukas, V. (2016): Management of iron overload in hemoglobinopathies: What is the appropriate target iron level? Annals of the NewYork Academy of Sciences, 1368(1), 95–106. https://doi.org/10.1111/nyas.13060.

Consalez, F.; Ahern, M.; Andersen, P. and Kjellevold, M. (2022): The Effect of the Meat Factor in Animal-Source Foods on Micronutrient Absorption: A Scoping Review. Advances in Nutrition, 13(6): 2305–2315. https://doi.org/10.1093/advances/nmac089.

Core, A. B.; Canali, S. and Babitt, J. L. (2014): Hemojuvelin and bone morphogenetic protein (BMP) signaling in iron homeostasis. Frontiers in Pharmacology, 5. https://www.frontiersin.org/articles/10.3389/fphar.2014.00104.

Daher, R.; Manceau, H. and Karim, Z. (2017): Iron metabolism and the role of the iron-regulating hormone hepcidin in health and disease. La Presse Médicale, 46(12, Part 2): e272–e278. https://doi.org/10.1016/j.lpm.2017.10.006.

Dalle-Donne, I.; Rossi, R.; Giustarini, D.; Milzani, A. and Colombo, R. (2003): Protein carbonyl groups as biomarkers of oxidative stress. Clinica Chimica Acta, 329(1): 23–

38. https://doi.org/10.1016/S0009-8981(03)00003-2.

Darvishi- Khezri, H.; Salehifar, E.; Kosaryan, M.; Aliasgharian, A.; Jalali, H. and Hadian Amree, A. (2016): Potential Effects of Silymarin and Its Flavonolignan Components in Patients with *β*-Thalassemia Major: A Comprehensive Review in 2015. Advances in Pharmacological and Pharmaceutical Sciences, e30463-73. https://doi.org/10.1155/2016/3046373.

Dev, S. and Babitt, J. L. (2017): Overview of iron metabolism in health and disease. Hemodialysis International. International Symposium on Home Hemodialysis, 21 Suppl 1(Suppl 1): S6–S20. https://doi.org/10.1111/hdi.12542.

Dixon, S. J. and Stockwell, B. R. (2014): The role of iron and reactive oxygen species in cell death. Nature Chemical Biology, 10(1): 9–17. https://doi.org/10.1038/nchembio.1416.

Dixon, S. J.; Lemberg, K. M.; Lamprecht, M. R.; Skouta, R.; Zaitsev, E. M.; Gleason, C. E. et al. (2012): Ferroptosis: An Iron-Dependent Form of Nonapoptotic Cell Death. Cell, 149(5): 1060–1072. https://doi.org/10.1016/j.cell.2012.03.042.

Drakesmith, H. and Prentice, A. M. (2012): Hepcidin and the iron-infection axis. Science (New York, N.Y.), 338(6108): 768–772. https://doi.org/10.1126/science.1224577.

Duarte, H. A. (2020): Iron - A Strategic chemical element that permeates history, economy, and society. Química Nova, 42: 1146–1153. https://doi.org/10.21577/0100-4042.20170443.

Duck, K. A. and Connor, J. R. (2016): Iron uptake and transport across physiological barriers. BioMetals, 29(4): 573–591. https://doi.org/10.1007/s10534-016-9952-2.

Eid, R.; Arab, N. T. T. and Greenwood, M. T. (2017): Iron mediated toxicity and programmed cell death: A review and a re-examination of existing paradigms. Biochimica Et Biophysica Acta. Molecular Cell Research, 1864(2), 399–430. https://doi.org/10.1016/j.bbamcr.2016.12.002.

Elsayed, M. E.; Sharif, M. U. and Stack, A. G. (2016): Transferrin Saturation: A Body Iron Biomarker. In G. S. Makowski (Ed.), Advances in Clinical Chemistry, 75: 71–97. Elsevier. https://doi.org/10.1016/bs.acc.2016.03.002.

Ems, T.; St Lucia, K. and Huecker, M.R. (2023): Biochemistry, Iron Absorption. [Updated 2023 Apr 17]. StatPearls [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448204/.

Entezari, S.; Haghi, S. M.; Norouzkhani, N.; Sahebnazar, B.; Vosoughian, F.; Akbarzadeh, D. et al. (2022): Iron Chelators in Treatment of Iron Overload. Journal of Toxicology, e4911205. https://doi.org/10.1155/2022/4911205.

Farid, Y.; Bowman, N. S. and Lecat, P. (2023): Biochemistry, Hemoglobin Synthesis. In StatPearls. StatPearls Publishing.

http://www.ncbi.nlm.nih.gov/books/NBK536912/.

Fishbane, S.; Mathew, A. and Vaziri, N. D. (2014): Iron toxicity: Relevance for dialysis patients. Nephrology Dialysis Transplantation, *29*(2): 255–259. https://doi.org/10.1093/ndt/gft269.

Fleming, R. E. and Ponka, P. (2012): Iron overload in human disease. The New England Journal of Medicine, 366(4):348–359. https://doi.org/10.1056/NEJMra1004967.

Fortes, G. B.; Alves, L. S.; De Oliveira, R.; Dutra, F. F.; Rodrigues, D.; Fernandez, P. L. etal. (2012): Heme induces programmed necrosis on macrophages through autocrine TNF and ROS production. Blood, 119(10): 2368–2375. https://doi.org/10.1182/blood-2011-08-375303.

Galaris, D.; Barbouti, A. and Pantopoulos, K. (2019): Iron homeostasis and oxidative stress: An intimate relationship. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, 1866(12): 118535. https://doi.org/10.1016/j.bbamcr.2019.118535.

Ganz, T. (2009): Iron in innate immunity: Starve the invaders. *Current Opinion in Immunology*, 21(1): 63–67. https://doi.org/10.1016/j.coi.2009.01.011.

Ganz, T. and Nemeth, E. (2006): Iron imports. IV. Hepcidin and regulation of body iron metabolism. American Journal of Physiology-Gastrointestinal and Liver Physiology, 290(2): G199–G203. https://doi.org/10.1152/ajpgi.00412.2005.

Ganz, T. and Nemeth, E. (2012): Hepcidin and iron homeostasis. Biochimica Et Biophysica Acta, 1823(9): 1434–1443. https://doi.org/10.1016/j.bbamcr.2012.01.014.

García-Pérez, J.; Fernández-Navarro, P.; Castelló, A.; López-Cima, M. F.; Ramis, R.; Boldo, E. et al. (2013): Cancer mortality in towns in the vicinity of incinerators and installations for the recovery or disposal of hazardous waste. Environment International, 51:31–44. https://doi.org/10.1016/j.envint.2012.10.003.

Góth, L.; Rass, P. and Páy, A. (2004): Catalase enzyme mutations and their association with diseases. Molecular Diagnosis, 8(3): 141–149. https://doi.org/10.1007/BF03260057.

Hassanzadeh, P.; Arbabi, E. and Rostami, F. (2014): The ameliorative effects of sesamol against seizures, cognitive impairment, and oxidative stress in the experimental model of epilepsy. Iranian Journal of Basic Medical Sciences, 17(2): 100–107.

Hentze, M. W.; Muckenthaler, M. U.; Galy, B. and Camaschella, C. (2010): Two to Tango: Regulation of Mammalian Iron Metabolism. Cell, 142(1): 24–38. https://doi.org/10.1016/j.cell.2010.06.028.

Hurrell, R. and Egli, I. (2010): Iron bioavailability and dietary reference values. The American Journal of Clinical Nutrition, 91(5): 1461S-1467S. https://doi.org/10.3945/ajcn.2010.28674F.

Imam, M. U.; Zhang, S.; Ma, J.; Wang, H. and Wang, F. (2017): Antioxidants Mediate Both Iron Homeostasis and Oxidative Stress. Nutrients, 9(7), 671. https://doi.org/10.3390/nu9070671.

Jenkitkasemwong, S.; Wang, C.-Y.; Coffey, R.; Zhang, W.; Chan, A.; Biel, T. et al. (2015): SLC39A14 Is Required for the Development of Hepatocellular Iron Overload in Murine Models of Hereditary Hemochromatosis. Cell Metabolism, *22*(1): 138–150. https://doi.org/10.1016/j.cmet.2015.05.002.

Jiang, L.; Kon, N.; Li, T.; Wang, S.-J.; Su, T.; Hibshoosh, H. et al . (2015): Ferroptosis as a p53-mediated activity during tumor suppression. Nature, 520(7545):7545. https://doi.org/10.1038/nature14344.

Jung, C. H.; Lee, M. J.; Hwang, J. Y.; Jang, J. E.; Leem, J.; Park, J.-Y. et al. (2013): Elevated Serum Ferritin Level Is Associated with the Incident Type 2 Diabetes in Healthy Korean Men: A 4 Year Longitudinal Study. PLoS ONE, 8(9): e75250. https://doi.org/10.1371/journal.pone.0075250.

Kawabata, H. (2019): Transferrin and transferrin receptors update. Free Radical Biology and Medicine, 133: 46–54. https://doi.org/10.1016/j.freeradbiomed.2018.06.037.

Kitsati, N.; Mantzaris, M. D. and Galaris, D. (2016): Hydroxytyrosol inhibits hydrogen peroxide-induced apoptotic signaling via labile iron chelation. Redox Biology, 10:233–242. https://doi.org/10.1016/j.redox.2016.10.006.

Knutson, M. D. (2017): Iron transport proteins: Gateways of cellular and systemic iron homeostasis. The Journal of Biological Chemistry, 292(31): 12735–12743. https://doi.org/10.1074/jbc.R117.786632.

Koren, A.; Fink, D.; Admoni, O.; Tennenbaum-Rakover, Y. and Levin, C. (2010): Non-transferrin bound labile plasma iron and iron overload in Sickle Cell Disease: A comparative study between Sickle Cell Disease and Î^2 thalassemic patients: Non-transferrin bound labile plasma iron and iron overload in SCD. European Journal of Haematology, 84(1): 72–78. https://doi.org/10.1111/j.1600-0609.2009.01342.x.

Koskenkorva-Frank, T. S.; Weiss, G.; Koppenol, W. H. and Burckhardt, S. (2013): The complex interplay of iron metabolism, reactive oxygen species, and reactive nitrogen species: Insights into the potential of various iron therapies to induce oxidative and nitrosative stress. Free Radical Biology and Medicine, 65: 1174–1194. https://doi.org/10.1016/j.freeradbiomed.2013.09.001.

Kruszewski, M. (2003): Labile iron pool: The main determinant of cellular response to oxidative stress. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 531(1): 81–92. https://doi.org/10.1016/j.mrfmmm.2003.08.004.

Krzystek-Korpacka, M.; Neubauer, K.; Berdowska, I.; Boehm, D.; Zielinski, B.; Petryszyn, P.; Terlecki, G. et al. (2008): Enhanced formation of advanced oxidation protein products

in IBD: Inflammatory Bowel Diseases, 14(6): 794–802. https://doi.org/10.1002/ibd.20383.

Kumral, A.; Gonenc, S.; Acikgoz, O.; Sonmez, A.; Genc, K.; Yilmaz, O. et al .(2005): Erythropoietin Increases Glutathione Peroxidase Enzyme Activity and Decreases Lipid Peroxidation Levels in Hypoxic-Ischemic Brain Injury in Neonatal Rats. Biology of the Neonate, 87(1): 15–18. https://doi.org/10.1159/000080490.

Liu, X. and Theil, E. C. (2005): Ferritins: Dynamic Management of Biological Iron and Oxygen Chemistry. Accounts of Chemical Research, 38(3): 167–175. https://doi.org/10.1021/ar0302336.

Lu, J.-B.; Jian, J.; Huang, W.; Lin, H.; Li, J. and Zhou, M. (2016): Experimental and theoretical identification of the Fe(vii) oxidation state in FeO_4^-. Physical Chemistry Chemical Physics, 18(45): 31125–31131. https://doi.org/10.1039/C6CP06753K.

Lunova, M.; Goehring, C.; Kuscuoglu, D.; Mueller, K.; Chen, Y.; Walther, P. et al. (2014): Hepcidin knockout mice fed with iron-rich diet develop chronic liver injury and liver fibrosis due to lysosomal iron overload. Journal of Hepatology, 61(3): 633–641. https://doi.org/10.1016/j.jhep.2014.04.034.

Meloni, A.; Puliyel, M.; Pepe, A.; Berdoukas, V.; Coates, T. D. and Wood, J. C. (2014): Cardiac iron overload in sickle-cell disease. American Journal of Hematology, 89(7): 678–683. https://doi.org/10.1002/ajh.23721.

Mendel, R. R.; Smith, A. G.; Marquet, A. and Warren, M. J. (2007): Metal and cofactor insertion. Natural Product Reports, 24(5): 963–971. https://doi.org/10.1039/B703112M.

Milman, N. T. (2020): A Review of Nutrients and Compounds, Which Promote or Inhibit Intestinal Iron Absorption: Making a Platform for Dietary Measures That Can Reduce Iron Uptake in Patients with Genetic Haemochromatosis. Journal of Nutrition and Metabolism, e7373498. https://doi.org/10.1155/2020/7373498.

Mobarra, N.; Shanaki, M.; Ehteram, H.; Nasiri, H.; Sahmani, M.; Saeidi, M. et al. (2016): A Review on Iron Chelators in Treatment of Iron Overload Syndromes. International Journal ofHematology-Oncology and Stem Cell Research, 10(4): 239–247.

Muckenthaler, M. U.; Galy, B. and Hentze, M. W. (2008): Systemic Iron Homeostasis and the Iron-Responsive Element/Iron-Regulatory Protein (IRE/IRP) Regulatory Network. Annual Review of Nutrition, *28*(1):197–213. https://doi.org/10.1146/annurev.nutr.28.061807.155521.

Ogun, A. S. and Adeyinka, A. (2023): Biochemistry, Transferrin. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK532928/.

Oni, J. and Nyokong, T. (2000): Interaction between iron(II) tetrasulfophthalocyanine and the neurotransmitters, serotonin, and dopamine. Polyhedron, 19(11):1355–1361. https://doi.org/10.1016/S0277-5387(00)00421-6.

Oyedeji, C. I.; Crawford, R. D. and Shah, N. (2021): Adherence to Iron Chelation Therapy with Deferasirox Formulations among Patients with Sickle Cell Disease and β-thalassemia. Journal of the National Medical Association, 113(2): 170–176. https://doi.org/10.1016/j.jnma.2020.08.007.

Paganoni, R.; Lechel, A. and Vujic Spasic, M. (2021): Iron at the Interface of Hepatocellular Carcinoma. *I*nternational Journal of Molecular Sciences, 22(8): Article 8. https://doi.org/10.3390/ijms22084097.

Pain, D. and Dancis, A. (2016): Roles of Fe–S proteins: From cofactor synthesis to iron homeostasis to protein synthesis. Current Opinion in Genetics & Development, 38:45–51. https://doi.org/10.1016/j.gde.2016.03.006.

Pantopoulos, K. (2004): Iron Metabolism and the IRE/IRP Regulatory System: An Update. Annals of the New York Academy of Sciences, 1012(1): 1–13. https://doi.org/10.1196/annals.1306.001.

Philpott, C. C. and Ryu, M.S. (2014): Special delivery: Distributing iron in the cytosol of mammalian cells. Frontiers in Pharmacology, 5. https://doi.org/10.3389/fphar.2014.00173.

Pietrangelo, A. (2016): Iron and the liver. Liver International, 36:116–123. https://doi.org/10.1111/liv.13020.

Pietrangelo, A.; Dierssen, U.; Valli, L.; Garuti, C.; Rump, A.; Corradini, E. et al. (2007): STAT3 Is Required for IL-6-gp130–Dependent Activation of Hepcidin In Vivo. Gastroenterology, 132(1): 294–300. https://doi.org/10.1053/j.gastro.2006.10.018.

Puliyel, M.; Mainous, A. G.; Berdoukas, V. and Coates, T. D. (2015a): Iron toxicity and its possible association with treatment of Cancer: Lessons from hemoglobinopathies and rare, transfusion-dependent anemias. Free Radical Biology and Medicine, 79:343–351. https://doi.org/10.1016/j.freeradbiomed.2014.10.861.

Raje, C. I.; Kumar, S.; Harle, A.; Nanda, J. S. and Raje, M. (2007): The macrophage cell surface glyceraldehyde-3-phosphate dehydrogenase is a novel transferrin receptor. The Journal of Biological Chemistry, 282(5): 3252–3261. https://doi.org/10.1074/jbc.M608328200.

Ramm, G. A. R. and Richard G. (2005): Hepatotoxicity of Iron Overload: Mechanisms of Iron-Induced Hepatic Fibrogenesis. Seminars in Liver Disease, 25(04): 433–449. https://doi.org/10.1055/s-2005-923315.

Salomao, M. A. (2021): Pathology of Hepatic Iron Overload. Clinical Liver Disease, 17(4): 232. https://doi.org/10.1002/cld.1051.

Sha, W.; Hu, F.; Xi, Y.; Chu, Y. and Bu, S. (2021): Mechanism of Ferroptosis and Its Role in Type 2 Diabetes Mellitus. Journal of Diabetes Research, e9999612. https://doi.org/10.1155/2021/9999612.

Shah, F. T.; Porter, J. B.; Sadasivam, N.; Kaya, B.; Moon, J. C. ; Velangi, M.

et al. (2022): Guidelines for the monitoring and management of iron overload in patients with haemoglobinopathies and rare anaemias. British Journal of Haematology, 196(2): 336–350. https://doi.org/10.1111/bjh.17839.

Shander, A.; Cappellini, M. D. and Goodnough, L. T. (2009): Iron overload and toxicity: The hidden risk of multiple blood transfusions. Vox Sanguinis, 97(3): 185–197. https://doi.org/10.1111/j.1423-0410.2009.01207.x.

Sies, H.; Berndt, C. and Jones, D. P. (2017): Oxidative Stress. Annual Review of Biochemistry, 86(1):715–748. https://doi.org/10.1146/annurev-biochem-061516-045037.

Silva, B. and Faustino, P. (2015b): An overview of molecular basis of iron metabolism regulation and the associated pathologies. *Bi*ochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1852(7):1347–1359. https://doi.org/10.1016/j.bbadis.2015.03.011.

Silvestri, L.; Nai, A.; Dulja, A. and Pagani, A. (2019):Hepcidin and the BMP-SMAD pathway: An unexpected liaison. In G. Litwack (Ed.), Vitamins and Hormones, 110:71–99. Academic Press. https://doi.org/10.1016/bs.vh.2019.01.004.

Singer, S. T.; Fischer, R.; Allen, I.; Lal, A.; Vichinsky, E.; Yuan, Q. and Wang, Z. J. (2020): Pituitary iron and factors predictive of fertility status in transfusion-dependent thalassemia. Haematologica, 106(6): 1740–1744. https://doi.org/10.3324/haematol.2020.252726.

Skolmowska, D. and Głąbska, D. (2019): Analysis of Heme and Non-Heme Iron Intake and Iron Dietary Sources in Adolescent Menstruating Females in a National Polish Sample. Nutrients, 11(5). https://doi.org/10.3390/nu11051049.

Su, L.-J.; Zhang, J.-H.; Gomez, H.; Murugan, R.; Hong, X.; Xu, D. et al. (2019): Reactive Oxygen Species-Induced Lipid Peroxidation in Apoptosis, Autophagy, and Ferroptosis. OxidativeMedicine and Cellular Longevity, 1–13. https://doi.org/10.1155/2019/5080843.

Suchdev, P. S.; Williams, A. M.; Mei, Z.; Flores-Ayala, R.; Pasricha, S.-R.; Rogers, L. M. et al. (2017): Assessment of iron status in settings of inflammation: Challenges and potential approaches. The American Journal of Clinical Nutrition, 106(6): 1626S-1633S. https://doi.org/10.3945/ajcn.117.155937.

Taher, A.; Cappellini, M. D.; Vichinsky, E.; Galanello, R.; Piga, A.; Lawniczek, T. et al. (2009): Efficacy and safety of deferasirox doses of >30 mg/kg per d in patients with transfusion-dependent anaemia and iron overload. British Journal of Haematology, 147(5): 752–759. https://doi.org/10.1111/j.1365-2141.2009.07908.x.

Td, C. (2014): Physiology and pathophysiology of iron in hemoglobin-associated diseases. FreeRadical Biology & Medicine, 72. https://doi.org/10.1016/j.freeradbiomed.2014.03.039.

Theil, E. C. (2012): Ferritin protein nanocages—The story. Nanotechnology Perceptions, 8(1): 7–16. https://doi.org/10.4024/N03TH12A.ntp.08.01.

Urbaniak, S. K.; Boguszewska, K.; Szewczuk, M.; Kaźmierczak-Barańska, J. and Karwowski, B. T. (2020): 8-Oxo-7,8-Dihydro-2′-Deoxyguanosine (8-oxodG) and 8-Hydroxy-2′-Deoxyguanosine (8-OHdG) as a Potential Biomarker for Gestational Diabetes Mellitus (GDM) Development. Molecules, 25(1): Article 1. https://doi.org/10.3390/molecules25010202.

Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M. T. D.; Mazur, M. and Telser, J. (2007): Free radicals and antioxidants in normal physiological functions and human disease. TheInternational Journal of Biochemistry & Cell Biology, 39(1): 44–84. https://doi.org/10.1016/j.biocel.2006.07.001,

Valková, V.; Ďúranová, H.; Bilčíková, J. and Habán, M. (2020): Milk Thistle (Silybum Marianum): : A Valuable Medical Plant With Several Therapeutic Purposes. Journal of Microbiology, Biotechnology and Food Sciences, 9(4):836–843. https://doi.org/10.15414/jmbfs.2020.9.4.836-843.

Wang, C.-Y. and Babitt, J. L. (2019): Liver iron sensing and body iron homeostasis. Blood, 133(1): 18–29. https://doi.org/10.1182/blood-2018-06-815894.

Wang, W.; Knovich, M. A.; Coffman, L. G.; Torti, F. M. and Torti, S. V. (2010): Serum ferritin: Past, present, and future. Biochimica Et Biophysica Acta, 1800(8): 760–769. https://doi.org/10.1016/j.bbagen.2010.03.011.

Wang, X.; Li, Y.; Han, L.; Li, J.; Liu, C. and Sun, C. (2021): Role of Flavonoids in the Treatment of Iron Overload. Frontiers in Cell and Developmental Biology, 9:685364. https://doi.org/10.3389/fcell.2021.685364.

Wrighting, D. M. and Andrews, N. C. (2006): Interleukin-6 induces hepcidin expression through STAT3. Blood, 108(9): 3204–3209. https://doi.org/10.1182/blood-2006-06-027631.

Yang, J.; Zhang, G.; Dong, D. and Shang, P. (2018): Effects of Iron Overload and Oxidative Damage on the Musculoskeletal System in the Space Environment: Data from Spaceflights and Ground-Based Simulation Models. International Journal of Molecular Sciences, 19(9): 2608. https://doi.org/10.3390/ijms19092608.

Yang, W.-P.; Chang, H.-H.; Li, H.-Y.; Lai, Y.-C.; Huang, T.-Y.; Tsai, K.-S. et al. (2020): Iron Overload Associated Endocrine Dysfunction Leading to Lower Bone Mineral Density in Thalassemia Major. The Journal of Clinical Endocrinology & Metabolism, 105(4): e1015–e1024. https://doi.org/10.1210/clinem/dgz309.

Yiannikourides, A. and Latunde-Dada, G. (2019): A Short Review of Iron Metabolism and Pathophysiology of Iron Disorders. Medicines, 6(3):85. https://doi.org/10.3390/medicines6030085.

Yun, S. and Vincelette, N. D. (2015): Update on iron metabolism and molecular perspective of common genetic and acquired disorder, hemochromatosis. Critical Reviews inOncology/Hematology, 95(1): 12–25. https://doi.org/10.1016/j.critrevonc.2015.02.006.

Zhang, C. (2014): Essential functions of iron-requiring proteins in DNA replication, repair, and cell cycle control. Protein & Cell, 5(10): 750–760. https://doi.org/10.1007/s13238-014-0083-7.

Zhong, H. and Yin, H. (2015): Role of lipid peroxidation derived 4-hydroxynonenal (4-HNE) in cancer: Focusing on mitochondria. Redox Biology, 4:193–199. https://doi.org/10.1016/j.redox.2014.12.011.