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Modulation of hepcidin synthesis: the core link in the bi-directional relationship between iron and obesity

Bilal Rah[1] · Rumaisa Rafiq[1] · Jasmine Sharafain[1] · Jibran Sualeh Muhammad[2] · Jalal Taneera[1,3] · Mawieh Hamad[1,4,5]

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Abstract

Over the past five decades, clinical and experimental data have established that iron metabolism, lipid metabolism, and obesity are intricately linked and differentially influence one another through complex metabolic pathways. Iron dyshomeostasis is now recognized as a key modulator of lipid metabolism, with profound implications for obesity and related metabolic disorders. Likewise, lipid metabolism and obesity significantly impact iron absorption and recycling. Although this interplay between iron metabolism, lipid metabolism, and obesity is complex, modulation of hepcidin synthesis seems to be the core link between these variables. As the global prevalence of metabolic disorders continues to escalate, understanding their multifactorial etiology has become a public health priority. Emerging evidence highlights the dysregulation of lipid metabolism as a central driver in the onset and progression of these conditions, with iron metabolism playing a crucial regulatory role. This review explores the relationship between iron metabolism on one hand and lipid metabolism and obesity on the other with specific emphasis on the molecular mechanisms underlying this relationship. The review also explores the bi-directional relationship between iron metabolism and mitochondrial functions, mainly energy production. It concludes by outlining the pathophysiological consequences of disrupted iron metabolism, vis-a-vis lipid metabolism, obesity, and diabetes. By synthesizing current knowledge, this review aims to provide new insights that could guide the development of novel therapeutic strategies to manage obesity, diabetes, and related metabolic disorders.

✉ Mawieh Hamad
mabdelhaq@sharjah.ac.ae

1 Iron Biology Research Group, Research Institute for Medical and Health Sciences, University of Sharjah, Sharjah, United Arab Emirates

2 Department of Biomedical Sciences, Birmingham Medical School, University of Birmingham, Edgbaston, Birmingham, UK

3 Department of Basic Medical Sciences, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates

4 Department of Medical Laboratory Technology, College of Health Sciences, University of Sharjah, Sharjah, United Arab Emirates

5 Department of Medical Laboratory Sciences, College of Health Sciences, University of Sharjah, Sharjah, UAE

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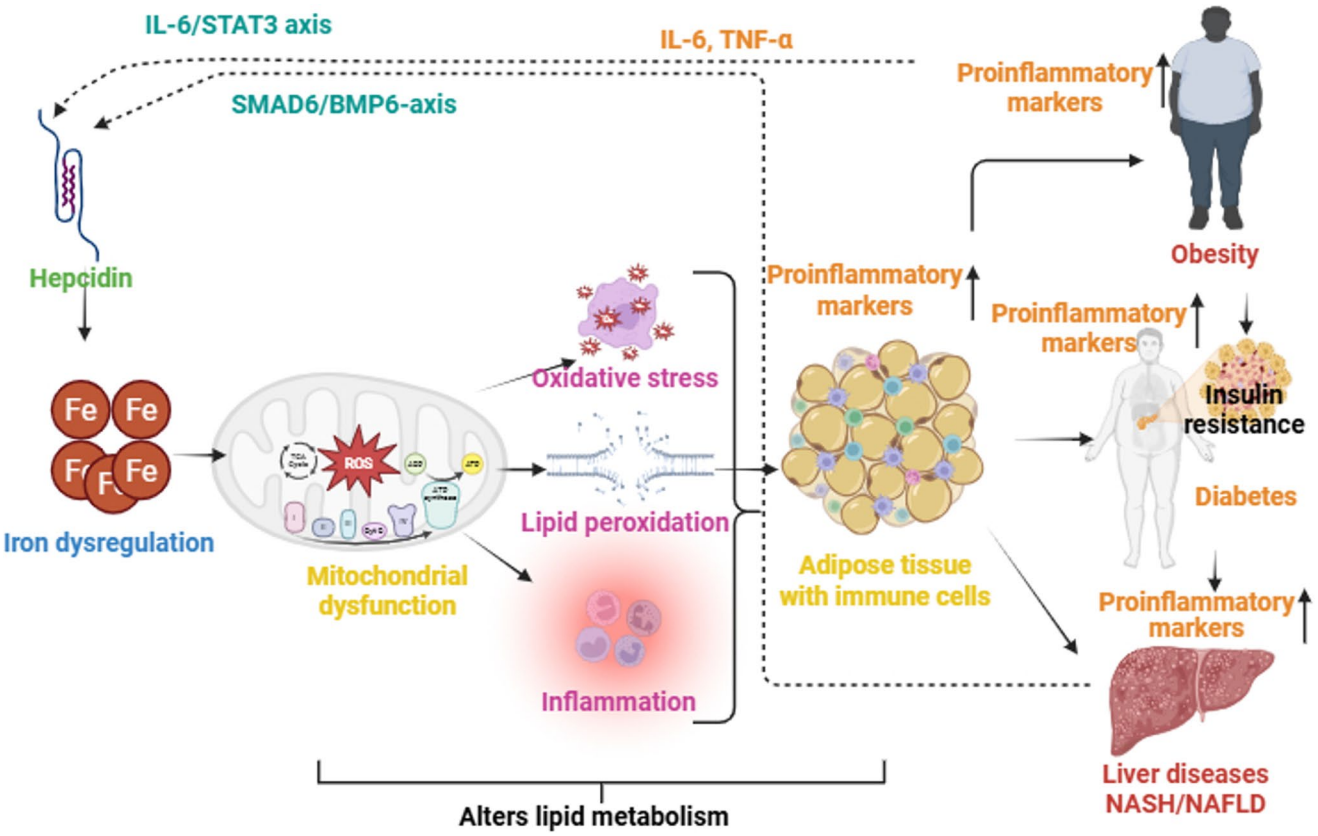
Graphical abstract



Keywords Iron metabolism · Lipid metabolism · Metabolic syndrome · Diabetes · Obesity

1 Introduction

Iron is an indispensable trace element required for the growth and survival of almost all living matters. It has a significant redox potential due to its ability to readily alternate between the reduced ferrous (Fe^{2+}) and oxidized ferric (Fe^{3+}) states. As such, iron serves as a cofactor in numerous proteins and molecules involved in oxygen transport, deoxyribose nucleic acid (DNA) replication, adenosine triphosphate (ATP) production, and the tricarboxylic acid (TCA) cycle (citric acid cycle or Krebs cycle), among other metabolic processes [1]. The diverse and pivotal roles iron plays in different metabolic processes notwithstanding, excess iron under aerobic conditions promotes the generation of reactive oxygen species (ROS) via Fenton chemistry, leading to oxidative stress and cellular damage [2]. The need to maintain iron availability while preventing iron overload (iron homeostasis) in mammalian systems is behind the evolution of intricate mechanisms that tightly regulate iron metabolism. Several organ systems collaborate to maintain iron homeostasis at the absorption, utilization, storage, release, and recycling levels [3]. The liver synthesizes the iron-regulatory peptide hormone hepcidin which targets and helps degrade the iron exporter ferroportin (FPN or SLC40A1), thereby inhibiting cellular iron release by iron-absorbing enterocytes, and iron-storing hepatocytes and macrophages [4]. The intestinal epithelium (mainly enterocytes) regulates dietary iron absorption, the bone marrow utilizes iron for heme synthesis, and the reticuloendothelial system (RES) facilitates the recycling of iron from senescent erythrocytes [3, 5]. This intricate interplay between these organ systems ensures that iron availability meets the body's metabolic needs while preventing iron overload. Iron dyshomeostasis, which is frequently observed in metabolic disorders like non-alcoholic fatty liver disease (NAFLD), obesity, and insulin resistance [6], is often referred to as dysmetabolic iron overload syndrome (DIOS) [7]. DIOS is characterized by steatosis, hepatic iron deposition, and significant alterations in iron regulatory pathways. Specifically, DIOS is associated with increased hepcidin and ferritin expression and decreased iron-exporting protein FPN expression on duodenal cells [8]. These changes lead to impaired intestinal iron absorption and poor systemic iron distribution.

Obesity is characterized by excessive adipose tissue accumulation, hence its potential to pose significant health risks, particularly in children, where its prevalence has now reached epidemic proportions [9]. Obesity is strongly associated with various comorbidities, including NAFLD, dyslipidemia, type 2 diabetes mellitus (T2DM), cardiovascular complications, chronic inflammation, and anemia [10]. It impacts several aspects of iron metabolism, influencing its regulation and triggering obesity-related anemia [11]. At the same time, several studies have elaborated on how disrupted iron metabolism promotes the development and progression of metabolic diseases [12–15]. Evidence linking iron metabolism to obesity is supported by a range of in vitro and animal studies, as well as clinical research involving people with obesity [13, 14]. Mitochondria, the primary sites for iron utilization, rely on an adequate supply of iron to maintain their proper function. Within the mitochondria, iron plays a critical role in heme synthesis, the formation of iron-sulfur (Fe-S) clusters, and the production of energy [16]. Iron dyshomeostasis can, therefore, severely compromise the functional integrity of the mitochondria, leading to metabolic dysfunction and potentially contributing to the development of various pathologies, including cancer, diabetes, and obesity [17, 18]. The link between iron and diabetes was initially observed in hereditary hemochromatosis and thalassemia, where iron overload is a hallmark feature [19, 20]. Excessive dietary iron intake and iron overload are now recognized as significant risk factors in diabetes [21]. Iron contributes to the pathogenesis of diabetes by promoting β-cell dysfunction and insulin resistance to pancreatic β-cells [22]. Furthermore, iron plays a regulatory role in metabolic processes within tissues critical for energy homeostasis, such as adipocytes, which act as iron sensors and modulate metabolic responses [23]. These findings underscore the importance of maintaining iron balance to prevent metabolic disorders and highlight the intricate relationship between iron metabolism and systemic health.

Focusing on obesity as the primary pathological driver illuminates its central role in dysregulated iron homeostasis through chronic, low-grade inflammation and adipose-derived hepcidin elevation [24, 25]. Excess adiposity promotes macrophage infiltration and secretion of interleukins such as adipokines (leptins), inlterleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), which upregulate hepcidin synthesis both systemically and directly within adipose tissue through morphogenetic protein (BMP)/SMA and MAD (SMAD)-related protein signaling cascades [6, 26]. Elevated hepcidin in obesity restricts iron absorption and release of iron hepatocytes and macrophages, thereby producing a paradoxical state of functional iron deficiency despite normal or elevated ferritin levels [27, 28]. High-fat diet (HFD)–induced obesity models corroborate this mechanism, showing increased tissue iron sequestration, suppressed FPN expression, and impaired iron recycling [6, 15]. Clinically, obese individuals consistently show higher hepcidin and ferritin compared to lean controls, independent of dietary iron intake, underscoring inflammation-driven iron maldistribution as a defining characteristic of obesity-related metabolic dysfunction [29].

2 Basics of iron metabolism

In basic terms, heme iron is absorbed via the heme carrier protein 1 (HCP-1) and non-heme iron is absorbed through the divalent metal transporter 1 (DMT1), both on the luminal side of the plasma membrane of duodenal enterocytes [30]. Increased demand for iron leads to reduced synthesis of hepcidin and the export of cellular iron to circulation via FPN. The major sources of iron in the circulation are iron-storing hepatocytes and macrophages; iron-absorbing enterocytes contribute a minimal (< 5%) amount of iron to the circulation. Iron in intestinal enterocytes, hepatocytes, and macrophages are utilized as Fe^{2+} form or stored as Fe^{3+} form in ferritin. Cells release Fe^{2+} iron, which is quickly oxidized to Fe^{3+} form by the action of the membrane-adjacent ferroxidases ceruloplasmin and/or hephaestin (Fig. 1) [31]. Fe^{3+} form of iron in the circulation binds the plasma iron carrying protein transferrin (apotransferrin; apo-TF) to form di-ferric transferrin (holo-TF). Circulating holo-TF binds the transferrin receptor 1 (TfR1) on target cells, and the complex is internalized via clathrin-coated vesicle-mediated endocytosis [32]. Once inside the cell, the endosome undergoes an acidification process driven by proton pumps to reduce the binding affinity of iron to transferrin (TF) and facilitate the release of Fe^{3+} iron [1]. Extracted Fe^{3+} form of iron in the endosome is reduced to ferrous by the six-transmembrane epithelial antigen of prostate 3 (STEAP3). Endosomal DMT1 and other pumping proteins then transport ferrous iron to be part of the labile iron pool (LIP) in the cytoplasm for utilization. Some of the Fe^{2+} iron in the cytoplasm is stored in ferritin or released via the iron exporter FPN [33]. TfR1 and apo-TF are recycled back to the surface. Some of the LIP iron is trafficked into the mitochondria, to serve as a cofactor in various mitochondrial for heme and Fe-S cluster synthesis and for the activity of several enzymes involved in energy production [34]. Fe-S clusters and heme play critical roles in mitochondrial function, serving as components in the electron transport chain (ETC) complexes I-III, cytochrome c, and aconitase (ACO1) within the TCA cycle [35].

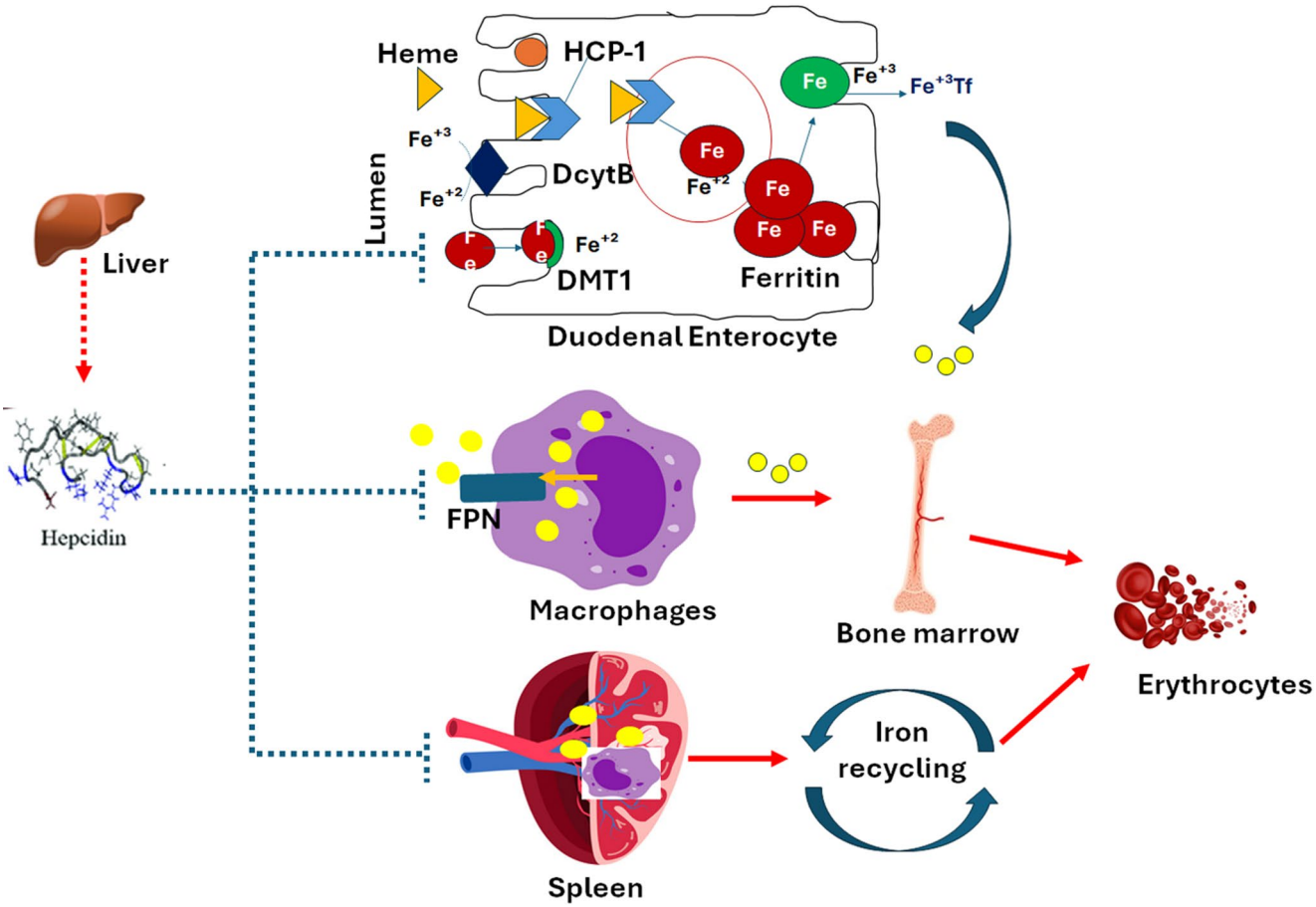


Fig. 1 Regulation of iron metabolism (absorption, transport, utilization, and recycling) by hepcidin. Dietary iron, primarily in the ferric form (Fe^{3+}), is reduced to the ferrous form (Fe^{2+}) by duodenal cytochrome B (DcytB) prior to absorption by duodenal enterocytes. Iron is taken up into enterocytes as Fe^{2+} or as heme-bound iron through heme carrier protein 1 (HCP-1). Within the enterocyte, iron is transiently stored as ferritin. When required, ferritin-bound iron is oxidized back to Fe^{3+} by hephaestin and subsequently binds to transferrin (Tf), an iron carrier protein responsible for transporting iron to various cells and tissues for utilization. Recycled iron, derived from the degradation of senescent erythrocytes, is taken up by macrophages of the reticuloendothelial system (RES) in the spleen. This recycled iron is then transported to the bone marrow for erythropoiesis or used as a cofactor for mitochondrial enzymes involved in numerous biochemical reactions

2.1 Systemic iron homeostasis

Systemic iron homeostasis is maintained mainly through the hepcidin-FPN axis, which regulates iron absorption by enterocytes and recycling by hepatocytes and splenic macrophages [4]. Hepcidin, a liver-derived peptide hormone, is the principal regulator of iron homeostasis [36] (Fig. 2). In addition to the liver, other tissues, including adipocytes, reticular macrophages, pancreatic β cells, and adipose tissue, also produce appreciable amounts of hepcidin [37]. Typically, the production of hepcidin increases in response to elevated hepatic iron levels, high plasma transferrin saturation, or inflammation. Its synthesis is modulated by a variety of physiological and pathological stimulus, including infection, inflammation, hypoxia, anemia, and steroids. To limit iron availability, hepcidin binds FPN, triggering its internalization, ubiquitination, and proteasomal degradation. This process restricts the ability of enterocytes, macrophages, hepatocytes, and other cells involved in iron absorption and recycling to release iron in the circulation [38]. Hepcidin expression is tightly regulated through multiple interconnected pathways, including the BMP/SMAD-related proteins signaling cascade, hemojuvelin (HJV), and pro-inflammatory cytokines such as IL-6. The BMP pathway is activated when BMP ligands bind to type I and type II BMP receptors, leading to the phosphorylation of SMAD 1/5/8 proteins. These phosphorylated SMADs then form complexes with SMAD4, which translocate to the nucleus to enhance hepcidin genes (*HAMP*) transcription.

HJV serves as a BMP co-receptor, amplifying the BMP signaling pathway and promoting hepcidin synthesis [39]. Moreover, the interaction between holo-TF and TfR1 facilitates the association of the homeostatic iron regulator (HFE) with transferrin receptor 2 (TfR2) and

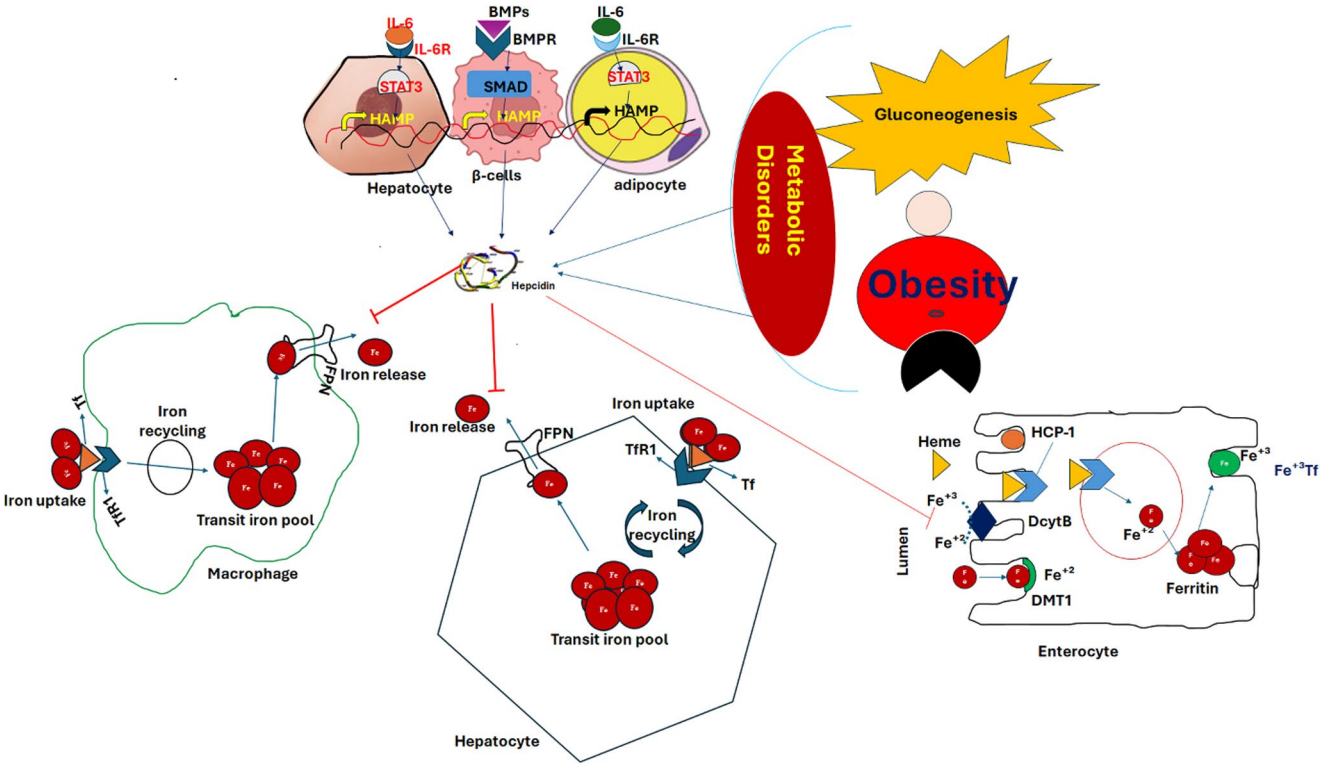


Fig. 2 A snippet of the bi-directional interplay between iron metabolism and metabolic disorders. Obesity-related inflammation and gluconeogenesis alter iron uptake, utilization, and absorption by dysregulating IL-6/STAT3 and BMP/SMAD signaling. This disrupts hepcidin synthesis in hepatocytes, pancreatic β-cells, and adipocytes leading to perturbed iron homeostasis, that exacerbates the progression and severity of metabolic disorders

BMP receptors, thereby modulating hepcidin expression. Inflammatory signals, such as IL-6, activate the Janus kinase 2 (JAK2)-signal transducer and activator of transcription (STAT3) pathway, leading to STAT3 phosphorylation and nuclear translocation, which further upregulates hepcidin transcription [40]. Therapeutic strategies targeting hepcidin, such as the use of hepcidin antagonists like lexaptepid pegol, have shown promise in mitigating inflammation-induced hypoferremia in lipopolysaccharide (LPS)-induced models, highlighting the potential of hepcidin modulation in addressing iron dysregulation during inflammation [41]. Hormonal regulation also plays a role, as elevated levels of 17-β estradiol (estrogen 2; E2) have also been shown to suppress *HAMP* gene expression, mainly through the interaction between E2/estrogen receptor complex and estrogen-responsive elements (EREs) in the *HAMP* gene promoter [42]. Furthermore, gluconeogenesis also activates the cereblon-Kruppel-like (CKL) factor 15 pathway, which promotes *HAMP* transcription and hepcidin synthesis [28]. Intriguingly, hepcidin synthesis decreases in mice with obesity particularly those induced by HFD, suggesting a link between iron regulation and energy metabolism [43].

2.2 Cellular iron homeostasis

Simultaneously, iron regulatory proteins (IRPs) dissociate from the 3'-untranslated region (UTR) of TfR1 messenger ribonucleic acid (mRNA), leading to its destabilization and reduced translation. Conversely, when cellular iron levels are low, IRPs bind to the 5'-UTR of *ferritin* and *FPN* mRNAs, inhibiting their translation to minimize iron storage and export, while binding to the 3'-UTR iron response elements (IREs) of *TfR1* mRNA stabilizes it and promotes translation to enhance iron uptake (22). The IRP-IRE system is a major regulator of cellular iron homeostasis. The IRP-IRE system exerts post-transcriptional control over the expression of key iron regulators, including TfR1, ferritin, and FPN, through its ability to modulate the stability of their mRNAs. The mRNAs of *TfR1*, *ferritin*, and *FPN* contain IREs within their 5'- or 3'-UTR, which serve as binding sites for IRPs. Under conditions of high cellular iron, IRPs dissociate from IREs in the 5'-UTR of *ferritin* and *FPN* mRNAs, allowing for their translation. Simultaneously IRPs also dissociate from the 3'-UTR of *TfR1* mRNA, leading to destabilization and blocking its translation. Conversely, when cellular iron levels are low, IRPs bind to the

5'-UTR of *ferritin* and *FPN* mRNAs, blocking their translation to reduce iron storage and export; binding of IRPs to the 3'-UTR IREs on *TfR1* mRNA allows for its translation to promote iron uptake [34]. In addition to the IRP-IRE system, epigenetic mechanisms such as methylation of the cytosine-phosphate-guanine (CpG) islands in the promoter regions of *TfR1* and *ferritin* genes were also shown to differentially regulate the expression of these genes depending on cellular iron levels among other triggers [44]. This dual-layered regulation combining post-transcriptional and epigenetic control ensures precise adaptation to fluctuating iron availability, highlighting the complexity and robustness of cellular iron homeostasis.

3 Iron and lipid metabolism

Lipid metabolism involves multiple biochemical pathways regulating its synthesis and degradation. It is primarily governed by three key processes: (1) the synthesis of fatty acids and triglycerides (lipogenesis), (2) the breakdown of triglycerides into free fatty acids (lipolysis), and (3) the oxidation of fatty acids for energy production (beta-oxidation) [45]. Homeostatic lipid metabolism helps to store energy and maintain the structural and metabolic integrity of body cells and tissues. The liver plays a central role in lipid metabolism by producing lipoproteins and facilitating the distribution of fatty acids throughout the body [46]. However, dysregulation of lipid metabolism, particularly the accumulation of lipids in non-adipose tissues such as the liver (ectopic fat), is strongly associated with the development and progression of metabolic disorders, including obesity and insulin resistance [47].

3.1 The link between iron and lipid metabolism

Numerous studies have shown that iron plays a critical role in lipid metabolism directly by serving as a cofactor for various enzymes involved in fatty acid oxidation and lipogenesis and indirectly through its effects on mitochondria and energy production and storage. Excess iron accumulation in the liver is a hallmark of NAFLD, where iron overload exacerbates hepatic inflammation and fibrosis [48]. Iron induces oxidative stress in hepatocytes, leading to cellular injury and inflammation [49, 50]. This oxidative stress, coupled with iron overload-associated lipid peroxidation and steatosis, drives the transition from NAFLD to non-alcoholic steatohepatitis (NASH) and liver fibrosis [51]. Consequently, maintaining liver iron homeostasis through interventions such as phlebotomy and iron chelation has emerged as a potential adjunctive treatment for NAFLD and NASH patients [52]. Animal studies have also demonstrated that iron overload significantly increases hepatic steatosis and the level of free fatty acids and triglycerides in blood plasma [11]. Iron overload also reported to promote lipogenesis and very low-density lipoprotein (VLDL) secretion from liver cells. High-iron diets (HID) were previously reported to increase hepatic lipid accumulation and disrupt hepatic insulin sensitivity [53]. In contrast, iron deficiency (ID) was reported to reduce intestinal absorption of lipids and disrupt lipid transport and metabolism [54]. Iron is also essential for the activity of key lipid metabolism-related enzymes, such as stearoyl-CoA desaturase, which introduces double bonds into saturated fatty acids, modulating cell membrane composition and fluidity [55]. Additionally, iron regulates the expression of genes involved in lipid metabolism encoding fatty acid synthase and acyl-CoA oxidase, hence balancing lipogenesis and lipolysis [56]. Interestingly, several studies have shown that changes in lipid metabolism influence iron metabolism. Lipid droplets in the liver and adipose tissues store both lipids and their composition dynamically change in response to metabolic states [56]. Increased levels of free fatty acids trigger inflammation, resulting in increased hepcidin synthesis and reduced iron release into the systemic circulation [28, 57, 58]. Adipose tissue also secretes several adipokines, including leptin and adiponectin, which play dual roles in regulating both lipids and iron metabolism. For example, leptin has been shown to modulate hepcidin synthesis, while adiponectin enhances iron uptake during erythropoiesis [59]. These interactions underscore the intricate crosstalk between iron and lipid metabolism, highlighting their collective impact on metabolic health and disease.

3.2 Iron and the mitochondria

Cellular energy production commences with glycolysis and the formation of pyruvate, which is transported into the mitochondrial matrix under aerobic conditions. Pyruvate is converted to acetyl coenzyme A (acetyl-CoA) to enter the mitochondrial TCA cycle. Similarly, fatty acids are transported to mitochondria as acyl-CoA and are broken down via beta-oxidation to generate acetyl-CoA. The entry of acetyl-CoA feeding into the TCA cycle facilitates the production of adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NADH) and the reduction of flavin adenine dinucleotide (FADH2). These molecules serve as electron donors in the ETC [60]. Within the ETC, NADH and FADH2 transfer electrons to a series of complexes (I–V), coenzyme Q, and cytochrome c [61], driving redox reactions that create a proton gradient across the inner mitochondrial membrane to power ATP production [16] (Fig. 3). Iron serves as a structural or catalytic component in key enzymes and proteins mediating these processes, including aconitase in the TCA cycle and cytochrome c in the ETC [62].

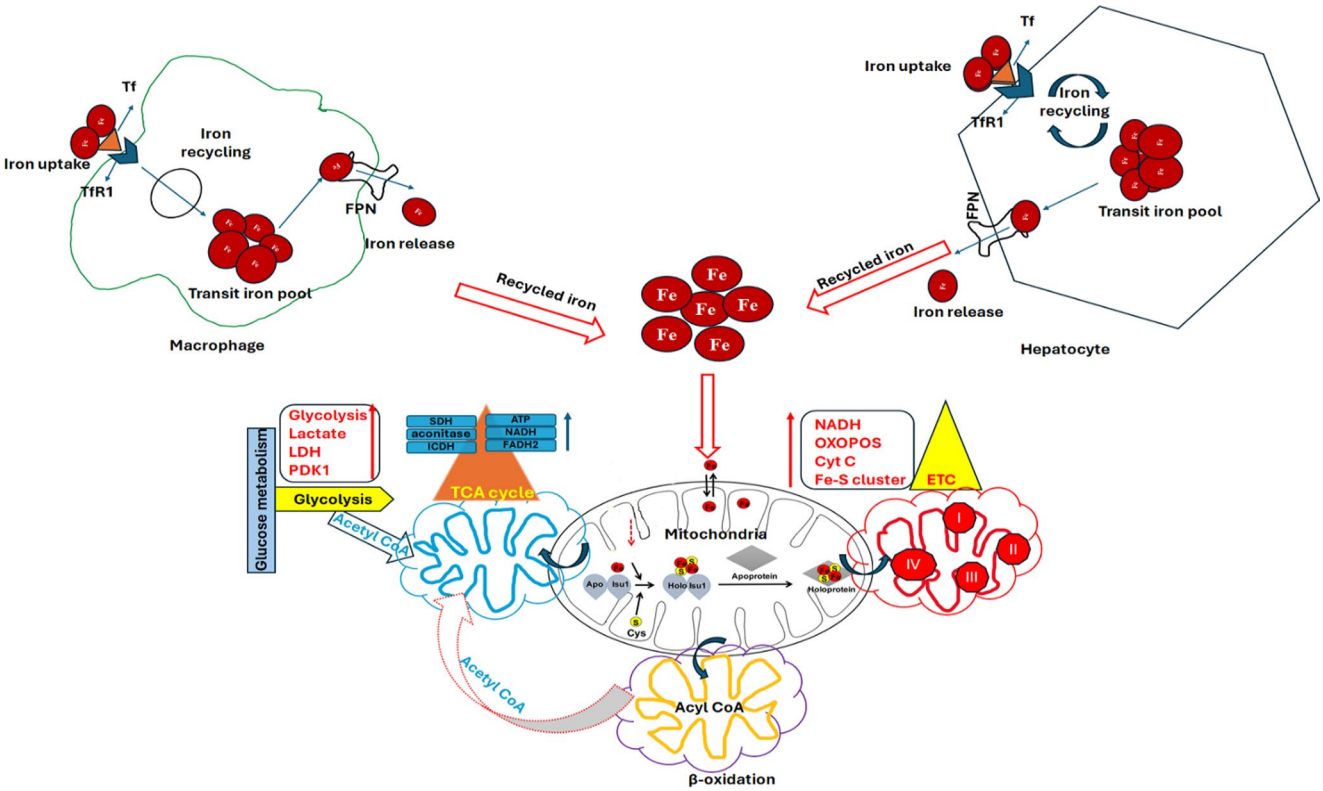


Fig. 3 The role of macrophages and hepatocytes in iron mobilization, utilization, and recycling. These cells facilitate heme synthesis and support mitochondrial function by supplying iron for essential enzymes involved in the tricarboxylic acid (TCA) cycle, the electron transport chain (ETC), and lipolysis through β-oxidation. This process ensures efficient energy production and cellular homeostasis

The synthesis of heme and Fe-S clusters, which take place in the mitochondrial matrix, is critical for hemoglobin (Hb) synthesis, the enzymatic activity of ACO1 in the TCA cycle, and the activity of several electron transfer proteins [28, 42]. For example, the heme group is an important prosthetic group in cytochrome c of the ETC [63], which allows cytochrome c to mediate reversible redox reactions that facilitate electron transfer during oxidative phosphorylation. Fe–S clusters, highly conserved prosthetic groups essential for ETC complexes I–III, DNA repair enzymes, and metabolic regulators, are synthesized in mitochondria. Iron overload-induced ROS oxidize and destabilize Fe–S clusters, impairing enzymes such as ACO1 in the TCA cycle and ETC complexes I–III. Additionally, oxidative damage to scaffold proteins like iron-sulfur cluster scaffold protein (ISCU) and chaperones such as frataxin disrupt Fe–S biogenesis and delivery, as observed in disorders like Friedreich's ataxia, which is characterized by mitochondrial iron accumulation and defective ETC activity [64, 65]. Such impairment leads to ATP depletion and further mitochondrial ROS generation, reinforcing oxidative stress [66, 67]. Conversely, iron deficiency limits substrate availability for Fe–S cluster assembly. Reduced iron impairs the activity of cysteine desulfurase NFS1 and mitoferrins (Mfrn1/2), crucial for iron import into the mitochondrial matrix. Inadequate Fe–S cluster synthesis compromises mitochondrial energy metabolism and activates IRPs, further perturbing cellular iron homeostasis. Defects in the export of newly formed Fe–S clusters or their derivatives via mitochondrial ABC transporters (ABCB7, ABCB8) also contribute to mitochondrial iron accumulation and cytosolic Fe–S cluster deficiency. Mutations in ABCB7, for instance, cause sideroblastic anemia and cerebellar ataxia, highlighting the systemic impact of mitochondrial iron dysregulation [68, 69]. Dysregulated iron homeostasis whether deficiency or overload profoundly compromises mitochondrial integrity, disrupting bioenergetics, organellar homeostasis, and redox signaling [70]. Excess labile iron within mitochondria catalyzes Fenton reactions, generating hydroxyl radicals (•OH) that peroxidize mitochondrial lipids and damage mitochondrial DNA (mtDNA) and proteins [71]. This oxidative burden destabilizes the mitochondrial membrane potential, leading to the opening of the mitochondrial permeability transition pore (mPTP). Subsequent mitochondrial swelling, outer membrane rupture, cytochrome c release, and ROS-induced ROS release (RIRR) create a vicious cycle that exacerbates oxidative stress and cellular damage [70, 71]. ID was previously associated with diminished expression of proteins

involved in mitochondrial respiratory chain complexes, particularly complex I (NADH oxidoreductase subunit A1, NDUFA1) and complex II (succinate dehydrogenase, SDH). This impairment contributes to defective mitochondrial oxidative phosphorylation and diminished energy production [72]. Additionally, reduced supply of Fe-S clusters further inhibits oxidative phosphorylation and contributes to the development of obesity [11]. Iron supplementation has been reported to alleviate mitochondrial structural abnormalities and enhance the expression of genes involved in oxidative phosphorylation [73], highlighting the importance of maintaining adequate iron levels for optimal mitochondrial function and energy metabolism. It was also reported to upregulate the expression of several mitochondrial respiratory chain complexes in liver and skeletal muscle cells, thereby supporting improved energy metabolism [74]. Moreover, iron supplementation has been shown to enhance mitochondrial function by upregulating the expression of genes involved in heme and Fe-S cluster biosynthesis. Key among these is hydroxymethylbilane synthase (HMBS), which plays a critical role in the heme biosynthetic pathway, and farnesyltransferase cytochrome c oxidase assembly factor 10 (COA10), which is essential for the assembly and function of cytochrome c oxidase in the ETC. Both HMBS and COA10 are vital for maintaining mitochondrial energy production and cellular metabolic homeostasis [75] (28, 51). Therefore, iron supplementation-driven uptake in heme synthesis may activate mitochondrial oxidative phosphorylation, promote energy expenditure, and minimize lipid accumulation with a net anti-obesity effect. In short, iron contributes to the management of cellular energy, mainly through its involvement in electron transport processes and the diverse set of mitochondrial functions that affect energy metabolism including the synthesis of heme and other iron-containing molecules that contribute to energy production in body cells [76]. Both ID and iron overload can disrupt these processes, leading to decreased energy output, fatigue, reduced exercise performance, and lipid accumulation, all of which contribute to obesity (40, 47). Mitochondrial dysfunction initiates a feedback cascade that impacts systemic iron regulation through hepcidin modulation. Excess mitochondrial reactive oxygen species (mtROS), generated under metabolic or hypoxic stress, stabilize hypoxia-inducible factor-1α (HIF-1α) by inhibiting its prolyl hydroxylases, linking mitochondrial redox changes to transcriptional control of hepcidin and iron exporters [77]. Stabilized HIF-1α can directly downregulate hepcidin expression as an adaptive response to preserve iron availability under oxidative stress. Concurrently, mitochondrial stress promotes the secretion of IL-6 from damaged or stressed tissues [78], activating JAK/STAT3 signaling in hepatocytes to induce hepcidin transcription [79], contributing to the anemia of inflammation [80]. Additionally, oxidative signals through elevated mtROS and downstream factors like p38-MAPK and C/EBPα upregulate hepatic hepcidin under iron-overload conditions, linking mitochondrial redox imbalance to systemic iron retention [81]. Together, these interconnected pathways illustrate how mitochondrial stress modulates hepcidin expression via HIF-1α suppression or IL-6/ROS-induced activation, thus influencing systemic iron homeostasis in a context-dependent manner.

3.3 Iron, adipose tissue, brown adipose tissue, macrophages, and thermogenesis

Iron metabolism plays an important role in adipose tissues, affecting adipocyte differentiation and metabolic health. In obesity and diabetes, adipose tissue exhibits dysregulated expression of iron-related genes, suggesting a link between iron homeostasis and adipose tissue dysfunction. Experimental studies suggest that intracellular iron availability is critical for adipogenesis. Iron depletion, via deferoxamine (DFO) or TF-knockdown, severely impaired adipocyte differentiation and elevated pro-inflammatory gene expression, whereas these effects that were reversed by iron supplementation [82]. Palmitate induced functional iron deficiency, which disrupted TF expression and iron uptake, while co-treatment with TF restored differentiation. Although iron overload also inhibited adipogenesis, its impact was less pronounced than that of iron deficiency. Coordinated expression of mitochondrial biogenesis and iron-regulatory genes highlights the role of iron in supporting mitochondrial function during adipogenesis. IRP1 expression and activity increased during differentiation in human and murine preadipocytes, whereas *IRP1* knockdown disrupted NADPH homeostasis, reduced lipogenic gene expression, and impaired adipogenesis. Both iron excess and depletion downregulated IRP1 expression, while *IRP1* loss impaired TfR-mediated iron uptake. Human studies corroborated these findings, showing positive correlations between IRP1, adipogenic markers, and TfR, and inverse associations with FPN [83]. Haem oxygenase-1 (HMOX1), a marker of oxidative stress and iron overload, was elevated in the adipose tissue of obese individuals and associated with inflammation, mitochondrial dysfunction, and metabolic derangements. Weight loss reduced HMOX1 expression, while weight gain and iron excess induced its upregulation, impairing mitochondrial respiration, glucose uptake, and adipogenesis [84]. Iron is critical for adipocyte differentiation through its role in epigenetic remodeling. Lysosome-mediated ferritinophagy supplies iron for early-stage histone and DNA demethylation at key adipogenic loci, including peroxisome proliferator-activated receptor gamma (PPARγ). Jumonji domain-containing 1 A (JMJD1A) and ten-eleven

translocation 2 (TET2) are emerging as key iron-dependent demethylases. Disruption of ferritin flux or iron chaperone activity impairs these epigenetic processes, highlighting the pivotal role of iron in orchestrating gene expression during adipogenesis [85]. Moreover, emerging evidence highlights the iron–inflammation axis as a key driver of adipose tissue dysfunction in obesity. Inflammatory cues, such as lipopolysaccharide (LPS), impair adipogenesis and induce adipocyte iron overload by enhancing iron uptake (TfR, SLC11A2) and storage (FTH1, FTL, LCN2), while suppressing iron export (FPN/SLC40A1). Transporters like SLC39A14, SLC39A8, and STEAP4 orchestrate this dysregulation [86].

Thermogenesis is a heat-generating process in primarily brown adipose tissue (BAT) that enhances the overall energy expenditure by oxidizing substrates within the mitochondria [87]. Previous work has shown that iron is essential for regulating mitochondrial fatty acid oxidation and BAT thermogenesis [88]. ID was reported to compromise the activity of iron-dependent enzymes critical for mitochondrial function, further altering BAT thermogenesis [89]. Additionally, ID resulting from defective IRP/IRE-dependent regulation of iron homeostasis within brown and beige adipocytes was previously reported to negatively affect the differentiation of brown adipocyte progenitors [90]. Furthermore, reduced expression of key components of the Fe-S cluster synthetic pathway, including cysteine desulfurase, ISCU, and bola-like 3 (BOLA3), have been linked to decreased mitochondrial fuel oxidation in BAT. This disruption contributes to metabolic dysregulation and obesity [28]. Knockdown of BOLA3 has been shown to impair thermogenesis in beige adipocytes, with its expression closely correlating with thermogenesis-associated genes, including uncoupling protein 1 (UCP1), a central regulator of heat production through mitochondrial oxidative phosphorylation [91]. Interestingly, iron supplementation was reported to enhance the expression of genes critical for Fe-S cluster synthesis, including ABCB7, Fe-S cluster assembly 2 (ISCA2), and BOLA3 [92] and alter the expression of several mitochondrial ETC genes that promote energy expenditure and attenuate weight gain [93]. Additionally, iron plays a critical role in adaptive thermogenesis within beige inguinal white adipose-tissue (iWAT) and BAT, yet its regulation remains unclear. Hepcidin knockout mice exhibit iron overload in both depots, with ferritin accumulation predominantly in stromal cells. While BAT thermogenesis remains intact, iWAT displays impaired beigeing, with reduced UCP1 expression, and diminished mitochondrial respiration, even after cold exposure [94]. These findings highlight iron dysregulation as a potential contributor to defective thermogenesis in iron overload disorders. Moreover, Adaptive thermogenesis requires efficient iron mobilization to support mitochondrial biogenesis during beige adipogenesis. β3-adrenergic stimulation activates hypoxia-inducible factor 2α (HIF2α) signaling, promoting erythropoietin production and splenic erythroid maturation, leading to hepcidin suppression and systemic iron redistribution into thermogenic fat [95]. Disruption of this iron-regulatory axis impairs beige fat development, highlighting coordinated renal hypoxia and hepcidin downregulation as key mechanisms linking systemic iron homeostasis to thermogenesis.

Iron availability in thermogenic brown and beige adipocytes affects heat generation and energy expenditure. These specialized cells convert the chemical energy stored in carbohydrates, fatty acids, and proteins into heat, particularly in response to cold weather [96]. Adaptive thermogenesis, a major contributor to total energy expenditure, is initiated by cold-induced activation of the sympathetic nervous system, leading to the release of norepinephrine, which then binds to β3-adrenergic receptors on BAT, stimulating the production of cyclic AMP (cAMP) [97]. Elevated cAMP levels activate protein kinase A (PKA), which drives the expression of key thermogenic genes such as UCP1, peroxisome proliferator-activated receptor-γ coactivator 1-alpha (PGC1-alpha), and PPARγ. This regulatory process occurs through p38 mitogen-activated protein kinase (p38 MAPK)-dependent and independent pathways, promoting the thermogenic function of BAT and beige adipocytes [98]. Mice with ID often exhibit reduced heat production and subsequent weight gain [43]. A reduction in the LIP content has been shown to hinder the differentiation of and mitochondrial biogenesis in brown and beige adipocytes [34]. Moreover, iron chelation in vivo has been found to inhibit brown adipocyte development and downregulate key genes involved in thermogenesis, including PRD1-BF1-RIZ1 homolog domain-containing 16, PPAR-alpha, PPAR-gamma, PGC1-alpha, and UCP1 [28]. Additionally, TfR1 deficiency in BAT was reported to trigger the differentiation of brown adipocyte precursors into white adipocytes and muscle cells, further underscoring the importance of iron in thermogenic regulation [99]. BMPs, which are involved in adipocyte differentiation, also play a significant role in thermogenesis. Specifically, BMP6 has been shown to promote BAT expansion under cold conditions by enhancing the differentiation of adipocyte precursors, further linking iron-related pathways to thermogenic regulation [63, 72]. These findings collectively underscore the importance of iron in supporting brown and beige adipocyte function, thermogenesis, and overall energy homeostasis, providing insights into the metabolic consequences of iron dysregulation (Fig. 4).

In adipose tissue, iron accumulation has been strongly linked to obesity-associated inflammation and insulin resistance, yet the mechanisms controlling iron distribution between adipocytes and resident immune cells remain incompletely understood. Emerging evidence highlights adipose

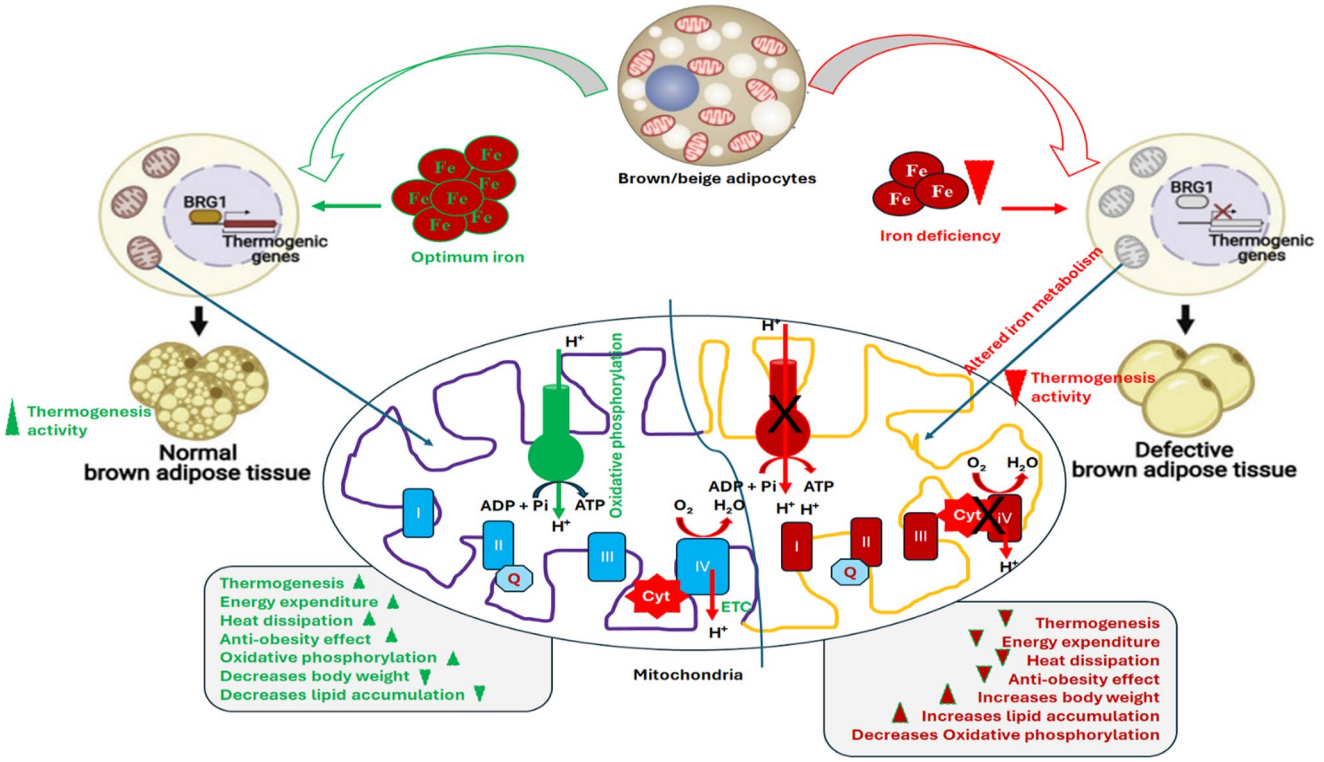


Fig. 4 Impact of iron dysregulation on thermogenesis in brown adipose tissue (BAT). Iron deficiency disrupts thermogenic processes by downregulating key thermogenic genes. This impairs mitochondrial function and reduces oxidative phosphorylation, thermogenesis, energy expenditure, and heat dissipation. Together, these changes compromise BAT's ability to counteract obesity, leading to lipid accumulation and weight gain

tissue macrophages (ATMs) as key regulators of iron homeostasis in adipose tissue. Studies using transgenic mouse models demonstrate that mitochondrial iron levels of macrophages influence systemic metabolism by modulating adipocyte iron content. Lowering mitochondrial matrix iron in macrophages promotes M2-like anti-inflammatory phenotypes, reduces adipocyte iron, and protects against HFD-induced metabolic dysfunction [100]. Conversely, increased macrophage mitochondrial iron content shifts ATMs toward a pro-inflammatory M1-like state, promotes adipocyte iron overload, and exacerbates obesity-related metabolic deterioration. In vitro studies further show that macrophage polarization alters iron trafficking between ATMs and adipocytes, with metabolically activated macrophages (MAM) promoting adipocyte iron accumulation and inflammation [101]. Macrophage-specific deletion of H-ferritin (FTH1) reduces macrophage iron storage capacity, attenuates adipose tissue inflammation, and protects mice from HFD-induced obesity and insulin resistance [102]. Moreover, adipocyte iron homeostasis critically influences systemic metabolism. TfR1-mediated iron uptake is selectively required across adipocyte subtypes, and its deletion protects mice from HFD-induced metabolic dysfunction. Reduced adipocyte iron improves white adipose tissue health and limits intestinal lipid absorption via altered vesicular transport in enterocytes. FPN overexpression mimics these protective effects, underscoring an adipocyte–enterocyte axis that regulates caloric influx and metabolic homeostasis [103]. Similarly, a subset of iron-rich MFe^{hi} ATMs acts as an iron sink, limiting adipocyte iron overload under conditions of dietary or systemic iron excess while maintaining a low inflammatory profile [104]. Together, these findings suggest that macrophage-mediated iron handling in adipose tissue is a critical determinant of metabolic health. Targeting macrophage iron metabolism may be a promising therapeutic strategy to alleviate obesity-related metabolic diseases by restoring adipocyte iron homeostasis and reducing tissue inflammation.

3.4 Hormonal influence on iron dysregulation

4 Pathological consequences of perturbed iron metabolism

Chronic low-grade inflammation, dysregulated adipose tissue metabolism, and insulin resistance are among the hallmark features of obesity. A growing body of research has elucidated the significant impact of disrupted iron metabolism on lipid metabolism, obesity, and diabetes.

4.1 Iron and obesity

Numerous studies have demonstrated that iron plays a significant role in regulating lipid metabolism in adipose tissues and that disruptions in iron metabolism may precipitate the physiological conditions that favor the onset of obesity and obesity-related metabolic disorders [114]. However, the relationship between obesity and iron status remains complex and unresolved. While some studies have found that obesity is associated with ID, potentially due to chronic inflammation and increased hepcidin levels that restrict iron absorption and recycling, others have reported that obesity correlates with iron overload, particularly in tissues such as the liver. A study involving women with obesity found that iron restriction was associated with decreased body weight and improved metabolic parameters [115]. Conversely, iron overloading has been shown to contribute to obesity by promoting inflammation, oxidative stress and lipid accumulation, while inhibiting adipocyte differentiation [56]. Epidemiological studies have established that individuals with obesity have increased serum levels of ferritin [11], suggesting that excess adipose tissue may enhance body iron sequestration, further complicating inflammation and metabolic dysfunction. Meta-analyses of 22 published reports have revealed that an increase in serum ferritin by one standard deviation leads to a 13.6% increase in the risk of developing obesity [11]. Similarly, a systematic review of 17 studies also reported that patients with obesity tend to have higher serum ferritin levels and TF saturation relative to non-obesity counterparts [116]. Moreover, serum FTH, a marker of iron storage, correlates positively with waist-to-hip ratio, visceral fat area, and waist-to-thigh ratio in healthy men [117].

In contrast, considerable clinical and epidemiological data have established that ID is approximately twice as common in overweight or patients with obesity of both children and adolescents relative to their average-weighing peers. Moreover, the incidence of ID was found to increase with higher body mass index (BMI) [15]. Interestingly, iron overloading in mice found to reduce visceral adipose tissue in the epididymal fat pads and iron accumulation in adipocytes [118]. On the other hand, a study involving 200 adults reported that iron supplementation reduces body weight and improves insulin sensitivity in individuals with ID anemia [119]. In patients with obesity of pregnant women, late-term iron absorption is often compromised, leading to reduced iron stores in infants [120]. ID is also more frequent in adult patients with obesity, particularly those undergoing bariatric surgery, due to micronutrient deficiency [121] (63, 64). TF saturation, an indicator of iron status, was reported to be lower in patients with obesity with large waist circumference than patients with obesity with smaller waist circumference [122]. Central obesity in overweight or patients with obesity in females was linked to decreased TF saturation, elevated hepcidin levels, and reduced absorption of supplementary iron [59]. A potential explanation for the observed association between obesity and reduced iron status is the relationship between central obesity and systemic low-grade inflammation [123]. A possible source of this confusion in understanding the relationship between obesity and iron status may relate to the complex interplay between the two conditions. In this regard, several studies have shown that obesity enhances hepcidin synthesis and blocks iron release from iron-absorbing enterocytes and iron-storing macrophages and hepatocytes, leading to low iron levels in the circulation [124]. This creates a state of functional ID, where despite high serum ferritin levels indicating iron overload in tissues, the body experiences insufficient bioavailable iron. This paradoxical condition exacerbates obesity and insulin resistance, contributing to the onset and progression of T2DM. Furthermore, iron-induced oxidative stress and inflammation disrupt insulin signaling pathways, further aggravating insulin resistance [125, 126].

Early intervention to correct iron dysregulation in obesity may play a critical role in preventing downstream metabolic complications. Obesity is frequently associated with altered iron metabolism characterized by low-grade inflammation and increased hepcidin production, leading to functional iron deficiency and impaired iron distribution across tissues [127]. Conversely, some individuals with obesity exhibit iron overload in metabolic organs such as the liver and pancreas, which promotes oxidative stress, lipid peroxidation, and exacerbation of insulin resistance [21]. Early normalization of iron status either through dietary modulation, controlled supplementation, or iron depletion therapies can mitigate adipose tissue dysfunction by reducing iron-driven adipocyte hypertrophy and pro-inflammatory adipokine secretion, while preserving insulin sensitivity [23]. Studies in both animal models and humans have shown that managing iron levels early in obesity reduces macrophage infiltration in adipose tissue and improves systemic glucose tolerance [11]. These findings highlight the potential of early iron-targeted strategies as adjunctive interventions to slow the progression from obesity to T2DM and NAFLD.

Iron homeostasis plays a dual role in metabolic diseases, necessitating a context-dependent approach to therapeutic intervention. Iron chelation is particularly beneficial in states of hepatic iron overload, such as DIOS and NAFLD, where excessive iron accumulation contributes to oxidative stress, mitochondrial dysfunction, and hepatocellular injury [128, 129]. In such cases, iron chelators like DFO or phlebotomy have shown promise in reducing liver iron content, improving insulin sensitivity, and attenuating inflammatory cytokine production [130]. Similarly, in chronic low-grade

inflammation associated with obesity or T2DM, where elevated hepcidin traps iron in macrophages and hepatocytes, chelation may relieve intracellular iron stress and restore proper metabolic signaling [21]. Conversely, iron supplementation is more appropriate in conditions of functional or absolute iron deficiency, frequently observed in obese women due to inflammation-driven hepcidin upregulation that limits dietary iron absorption and mobilization [11]. In such contexts, carefully calibrated iron supplementation can correct anemia, enhance physical performance, and support immune and cognitive function, provided that inflammatory markers are monitored to avoid exacerbating metabolic risk. Thus, a tailored approach guided by serum ferritin, TF saturation, hepcidin levels, and inflammatory markers is essential to determine whether iron depletion or repletion is more appropriate, with the goal of restoring systemic and tissue-specific iron balance while minimizing metabolic harm.

Biomarkers such as ferritin, TF saturation, soluble transferrin receptor (sTfR), and hepcidin serve as critical tools in guiding personalized iron interventions, particularly in the context of metabolic and inflammatory diseases. Ferritin reflects total body iron stores but is also an acute-phase reactant, often elevated during systemic inflammation, which can mask underlying iron deficiency especially common in obesity, T2DM, and chronic liver disease [127]. TF saturation provides complementary information about circulating iron availability but can also be influenced by inflammatory status and hepatic dysfunction. In contrast, hepcidin, a central regulator of systemic iron homeostasis, responds acutely to both iron overload and inflammatory signals. Elevated hepcidin restricts iron absorption and mobilization by downregulating FPN, and its measurement has been shown to predict the response to oral versus intravenous iron therapy [131]. Low hepcidin levels, often observed in absolute ID, indicate a greater likelihood of response to oral iron, while high hepcidin suggests poor absorption and favors parenteral routes or chelation strategies in overload conditions. Furthermore, the sTfR/ferritin index improves diagnostic accuracy by distinguishing iron deficiency anemia from anemia of chronic disease, particularly in individuals with coexisting inflammation [132]. In conclusion, the integration of ferritin, TF saturation, hepcidin, and sTfR into clinical practice enables nuanced, biomarker-driven approaches to iron therapy. Such personalized strategies not only enhance therapeutic efficacy but also minimize the risks associated with inappropriate iron supplementation or chelation in metabolically compromised individuals.

Recent advances in modulating systemic iron homeostasis have yielded several promising therapeutic candidates, including hepcidin agonists/antagonists, ferroportin modulators, and combination strategies that integrate metabolic and iron pathways. Hepcidin agonists, such as minihepcidins, a short synthetic peptides mimicking the active N-terminal segment of hepcidin and TMPRSS6 inhibitors (e.g., ALN-TMP), enhance endogenous hepcidin production to curtail pathological iron absorption and ameliorate tissue iron overload in conditions like hereditary hemochromatosis and β-thalassemia [133–138]. Among these, rusfertide and the small molecule VIT-2763 (vamifeport) have progressed to human clinical trials, where they demonstrate efficacy in reducing serum iron and transfusion requirements [139, 140]. Conversely, hepcidin antagonists (e.g., Lexaptepid pegol/NOX-H94, PRS-080) disrupt hepcidin-FPN interaction to mobilize sequestered iron in anemia of chronic disease or iron-limited metabolic states [134]. FPN stabilizers, notably vamifeport, which competes with hepcidin at the FPN binding site have demonstrated a novel mechanism whereby FPN is stabilized in its outward-facing conformation, thereby preventing iron overload and retaining iron balance [136, 141]. In metabolic disease contexts such as NAFLD, interventions that upregulate FPN expression via AMPK activation such as metformin, have been shown to restore hepatic iron export and reduce ferroptosis-induced tissue damage [138]. Emerging combination therapies that concurrently modulate iron and metabolic pathways through hepcidin modulation, FPN stabilization, and metabolic reprogramming (e.g., via AMPK agonists), are under exploration to synergistically ameliorate iron-driven oxidative stress, improve insulin sensitivity, and reduce hepatic steatosis. Therefore, the pipeline of iron-centric therapeutics now spans hepcidin mimetics, antagonists, FPN stabilizers, and combination regimens. Fine-tuning these interventions based on patient-specific iron and metabolic profiles holds great promise for addressing complex conditions at the intersection of iron overload, inflammation, and metabolic dysfunction.

Dietary modulation offers a viable adjunct to pharmacological strategies for managing iron-linked metabolic dysfunctions, with interventions such as iron-restricted diets, targeted supplementation, and micronutrient co-modulation under active investigation. In rodent models, both iron restriction and chelation have demonstrated protective effects against insulin resistance and β-cell failure in genetically obese mice, particularly when used early in the course of disease [142]. Contrastingly, iron supplementation in iron-deficient HFD mice improved mitochondrial function, increased β-oxidation-related gene expression in liver and muscle, reduced hepatic steatosis, and attenuated weight gain [28, 74]. Human cohort studies further suggest that intermediate dietary iron intake (~ 14 mg/day) is associated with a significantly reduced risk of T2DM, particularly among individuals with obesity, underscoring the importance of balanced intake [143]. Moreover, co-modulation of micronutrients such as combining iron with vitamin A,

zinc, or copper has been shown to synergistically influence energy metabolism and gut microbial profiles in animal models of undernutrition [144]. Critically, the metabolic impact of dietary iron varies depending on baseline iron status, genetic background, and presence of inflammation, making personalized dietary planning essential. In conclusion, nutritional interventions ranging from iron restriction to supplementation and micronutrient co-modulation offer promising, context-specific strategies to fine-tune iron availability and metabolic health. Tailoring these dietary approaches according to individual iron biomarkers, metabolic phenotypes, and genetic predisposition may optimize prevention and treatment of metabolic diseases linked to iron dysregulation.

4.2 The role of iron in the development of NAFLD

The worldwide prevalence of NAFLD now stands at approximately 25%, a trend that closely parallels that of obesity. Recent epidemiological trends suggest that NAFLD is occurring at high prevalence in the young; it is fast becoming the most prevalent chronic liver disease across children and adults of diverse racial and ethnic backgrounds. Obesity contributes to the development and progression of NAFLD, irrespective of whether the individual is metabolically healthy or unhealthy. Moreover, hepatic steatosis, or fat accumulation in the liver, is a common consequence of obesity and metabolic syndrome [145]. Consumption of HFD has been associated with increased body weight and elevated liver lipid content, exacerbating the risk of NAFLD [146]. Previous work has shown that iron supplementation may help reduce liver lipogenesis and lipid accumulation and mitigate hepatic steatosis [147]. Elevated serum ferritin levels are becoming a hallmark of iron dyshomeostasis in NAFLD. Greater than 30% of NAFLD patients exhibit serum ferritin concentrations exceeding the normal ranges (24–336 ng/mL in men and 11–307 ng/mL in women). Elevated ferritin levels in NAFLD may reflect increased liver iron storage, potentially contributing to oxidative stress and inflammation [129]. Delayed initial onset of steatosis is a common feature in patients with certain risk factors, including obesity, T2DM, and dyslipidemia. Often, delayed initial onset of steatosis is marked by mild iron accumulation within hepatic reticuloendothelial cells and hyperferritinemia [148] (Fig. 5). NAFLD patients with iron overload generally exhibit low levels of FPN in liver and duodenal tissues [149]. The resulting iron retention often accompanies decreased duodenal iron absorption in NAFLD patients. Dietary iron insufficiency in patients with obesity can exacerbate low FPN expression, limiting iron export from liver cells [150]. Additionally, Kupffer cells in the liver phagocytize damaged erythrocytes, increasing heme iron accumulation, which promotes oxidative stress and inflammation [151]. This process has been demonstrated in in vitro studies involving erythrophagocytosis and in vivo using HFD-fed rabbits [152]. Despite these observations, a randomized cohort study reported that reducing iron levels through bloodletting does not significantly improve delayed initial onset of steatosis patient's hepatic or metabolic health markers. Moreover, in vitro studies that assessed the effects of iron on hepatocytes showed that iron supplementation suppressed the expression of key lipogenic enzymes, such as fatty acid synthase and acetyl-CoA carboxylase, thereby reducing lipid synthesis [153]. Prolonged iron exposure (>24 h) in AML12 hepatocytes or primary human hepatocytes was reported to increase lipid accumulation [154]. In short, weight management through diet and lifestyle adjustments remains the primary intervention for managing delayed initial onset of steatosis [7].

4.3 Iron and diabetes

Diabetes or chronic hyperglycemia due to insufficient insulin production or insulin resistance ranks among the most prevalent chronic diseases [155]. According to the 2021 Diabetes Atlas of the International Diabetes Federation (IDF), approximately 537 million adults worldwide are affected by diabetes; this figure is projected to rise to 643 million by 2030 and 783 million by 2045 [156]. Clinical studies have established a significant link between iron dyshomeostasis and diabetes, particularly gestational diabetes. Evidence indicates that hyperferritinemia is associated with increased insulin resistance and a high risk of diabetes [157]. Additionally, elevated body iron levels in patients with obesity have been shown to increase the risk of T2DM, possibly due to the combined effects of inflammation and altered lipid metabolism [126]. In animal studies, iron-overloaded mice, such as those in hemochromatosis models, frequently exhibit increased adiposity and insulin resistance compared to normal mice [158]. Conversely, iron-deficient mice demonstrate reduced adiposity and enhanced glucose tolerance [125]. Excess iron promotes the generation and propagation of ROS and oxidative stress, resulting in lipid peroxidation and the formation of toxic lipid metabolites. These metabolites can disrupt insulin signaling pathways, contributing to insulin resistance [159].

Excessive pancreatic iron negatively impairs insulin secretion by promoting oxidative stress, inflammation, and β-cell dysfunction [160]. In contrast, reduced iron availability in the pancreatic milieu may alleviate oxidative stress and improve symptoms in patients with diabetes [161]. In other words, oxidative stress is widely considered a primary link between iron overload and patients with diabetes. Moreover, high iron levels have been shown to trigger

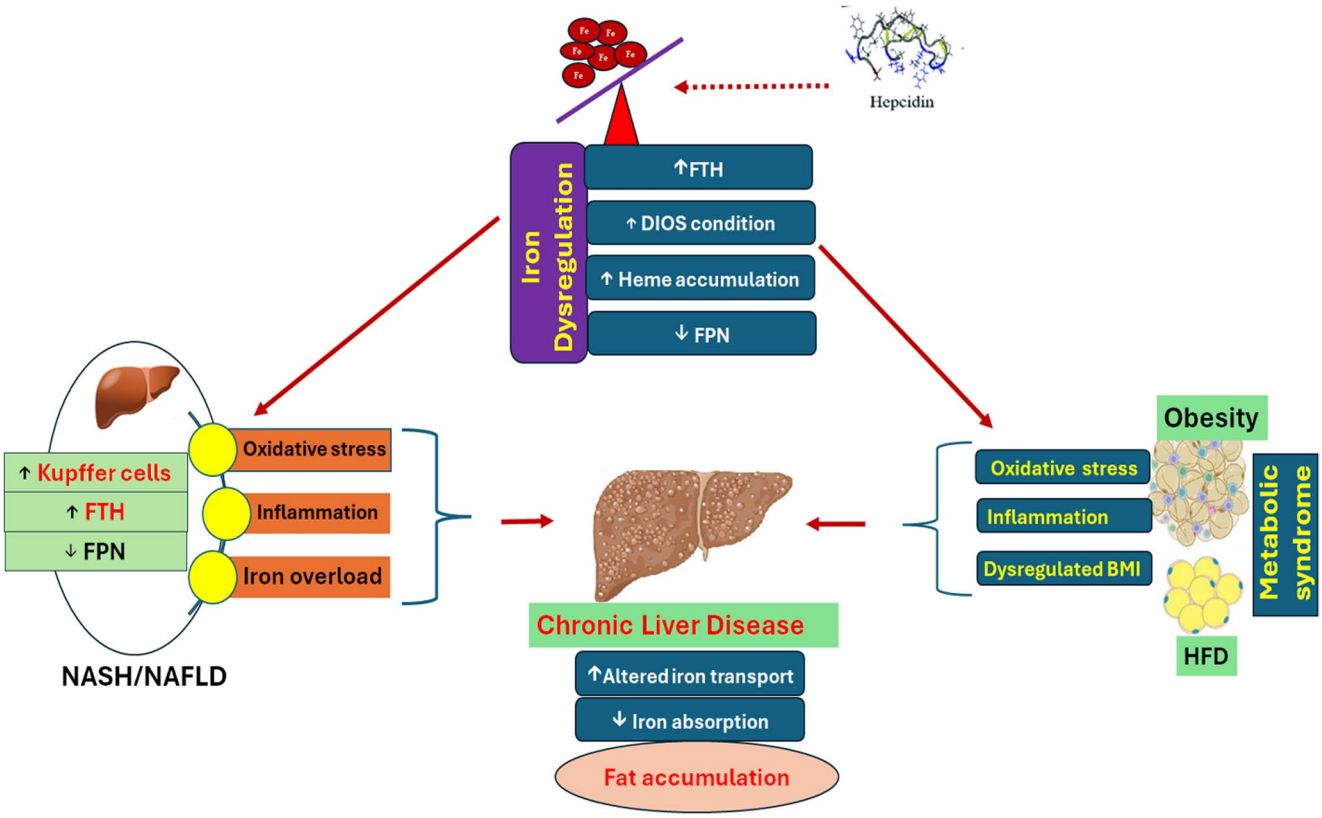


Fig. 5 Impact of iron dysregulation on the progression of NAFLD/NASH and chronic liver disease. Iron dysregulation, driven by obesity, dietary modifications, enhanced lipogenesis, and chronic inflammation, leads to the development and progression of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Iron overload in hepatocytes promotes oxidative stress, mitochondrial dysfunction, and lipid peroxidation, exacerbating hepatic fat accumulation and insulin resistance and increasing the risk of cirrhosis and chronic liver disease

oxidative damage and disrupt insulin secretion in pancreatic β-cells by downregulating synaptosome-associated protein 25 (SNAP25), a key protein in the insulin exocytosis pathway [162]. Mouse models with severe iron overload, due to hepcidin resistance or genetic alterations in iron regulatory genes (e.g., the p.C326S mutation in FPN or HAMP and HJV knockouts), were shown not to develop in patients with diabetes, possibly due to increased anti-oxidative potential [163]. In diabetes, ROS can target transcription factors essential for insulin gene regulation, such as V-Maf (an oncogene) and pancreatic and duodenal homeobox 1 (PDX1) [164]. Reduced hepcidin expression in β-cells, as observed in MIN6 cells where iron overload and decreased PDX1 expression were evident, impairs insulin synthesis [165]. Moreover, oxidative stress induced by iron overload modulates the expression of stress-response genes like HO-1 [166], which contains a GT-rich sequence in its promoter region that is regulated by transcription factors such as nuclear factor κB (NF-κB) and activator protein 2 (AP-2) [167] (Fig. 6). Chronic hyperglycemia significantly activates HO-1, increases iron storage, and promotes oxidative stress, thus contributing to T2DM progression [168]. These observations highlight the complex interplay between iron dysregulation, oxidative stress, and insulin production in diabetes.

Iron overload also exacerbates β-cell dysfunction through interactions with amylin, a polypeptide that aggregates within β-cells and disrupts cellular homeostasis in the great majority (>90%) of T2DM cases [160]. Iron promotes amylin aggregation, leading to oxidative stress, mitochondrial damage, and impaired insulin production [169]. Heme can bind amylin, resulting in H_2O_2 production and further ROS-mediated β-cell damage [170]. It is well established that activated AMP-activated protein kinase (AMPK) in the liver and skeletal muscle mitigates insulin resistance [171, 172] by promoting glucose uptake, enhancing fatty acid oxidation in peripheral tissues, and improving metabolic function and energy balance. AMPK-dependent reduction in hyperglycemia and the normalization of lipid metabolism make AMPK a potential therapeutic target for managing insulin resistance and metabolic disorders [173]. Iron overload in hemochromatosis models was reported to impair glucose oxidation and induce AMPK phosphorylation in skeletal muscles [174].

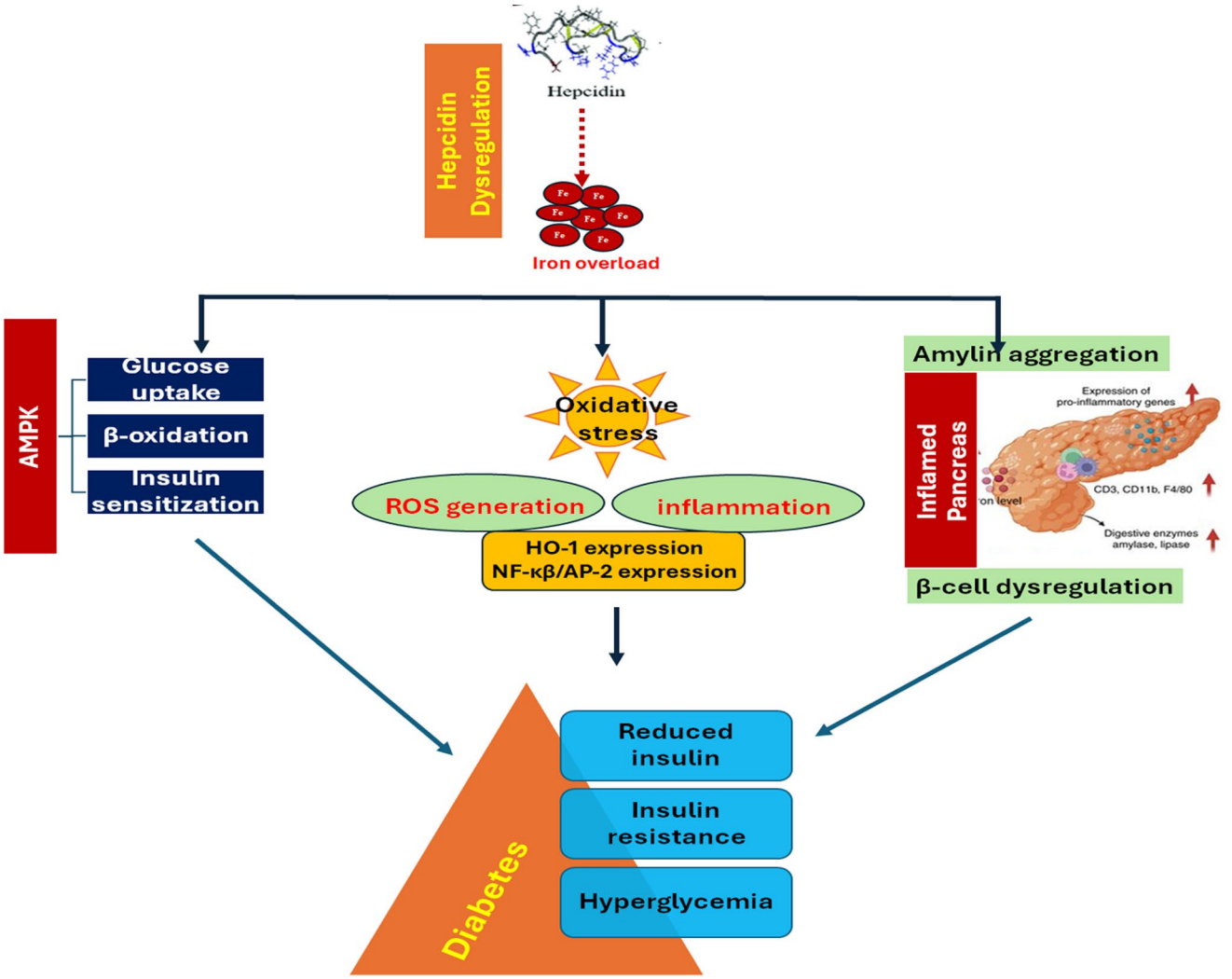


Fig. 6 Iron dyshomeostasis and pancreatic β-cells. Excess iron accumulation in pancreatic β-cells generates reactive oxygen species (ROS), which cause cellular damage and impair insulin secretion. This accelerates the formation of amyloid aggregates, further contributing to β-cell toxicity and loss of functional cell mass, ultimately leading to insulin insufficiency and the onset of diabetes

5 Modulation of Hepcidin is the key link between iron and obesity

As mentioned earlier, hepcidin is crucial in the connection between iron and obesity. This has been demonstrated by the observation that individuals with high BMI have significantly increased serum hepcidin levels [175].

5.1 Chronic inflammation and Hepcidin in obesity

The chronic, low-grade inflammation that characterizes obesity results in increased production of several pro-inflammatory cytokines, including TNF-α, interleukin-1beta (IL-1β), and IL-6 [176]. These cytokines increase hepcidin synthesis through STAT signaling and exacerbate ID in patients of obesity [177] (68, 71). M1 macrophages, which increase in hypertrophic or dysfunctional adipose tissue in obesity, release pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 [178]. Adipose tissue-derived IL-6 has been extensively studied for its role in regulating iron during inflammation and malnutrition [15]. TNF-α also influences iron homeostasis by modulating hepcidin expression; increased TNF-α expression has been shown to stimulate hepcidin production, while TNF-α inhibitors can reduce hepcidin levels, improving anemia. TNF-α gene expression in the liver negatively correlates with hepatic iron and ferritin levels [112]. Weight loss was reported to improve iron status in patients of obesity, likely by downregulating hepcidin synthesis and restoring systemic iron homeostasis [88]. Additionally, the expression of IL-6 and synthesis of hepcidin in visceral adipose tissues was reported to be significantly higher in rodents on HFD relative to counterparts on a normal diet [13]. In vitro studies with adipose tissue explants further revealed that hepcidin is expressed at both

the mRNA and protein levels in adipose tissue, suggesting that adipose tissue may contribute to systemic iron regulation [179]. Elevated hepcidin mRNA levels in the adipose tissue of patients of obesity were also reported to associate with increased IL-6 and other inflammatory markers, leading to obesity-related ID or "inflammatory hyposideremia" [6]. Furthermore, increased HMOX1 expression in mice with obesity was reported to inhibit hepcidin expression and reduce IL-6 and TNF-α production by liver cells [6].

5.2 Hemojuvelin and Hepcidin in obesity

Hemojuvelin (HJV), also called HFE2 or repulsive guidance molecule C (RGMC), a glycoprotein expressed in various tissues, including skeletal muscle, liver, heart, and adipocytes, plays a crucial role in hepcidin gene (*HAMP*) expression through its interaction with the BMP6/SMAD signaling pathway (31, 76, 78). HJV deficiency and antibodies targeting HJV were shown to disrupt BMP/SMAD signaling, leading to reduced hepcidin expression [134]. Soluble HJV levels are significantly elevated in patients with obesity, suggesting that adipose tissue may contribute to erythropoiesis and iron regulation in obesity [6]. High HJV expression in the adipose tissue of patients with obesity may promote hepcidin overproduction and exacerbate ID (Fig. 7). Interestingly, TNF-α downregulates HJV expression and reduces liver FTH production independent of BMP/SMAD signaling pathway [180].

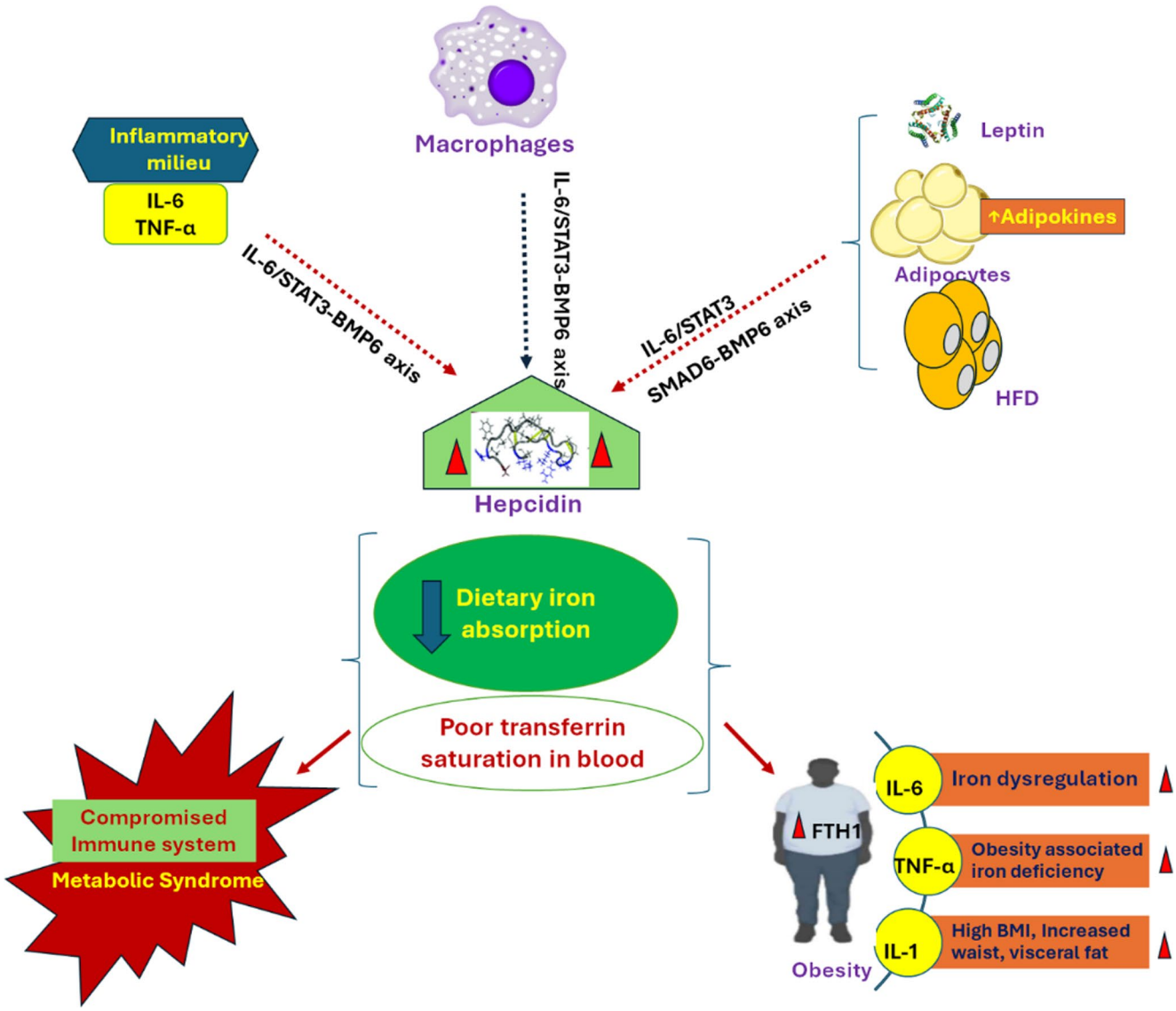


Fig. 7 Hepcidin at the center of the vicious cycle that involves impaired iron regulation, compromised immunity, and metabolic dysfunction. Chronic inflammation upregulates hepcidin synthesis and reduces dietary iron absorption, thus impairing transferrin-mediated iron transport. These changes compromise immune function and alter lipid metabolism, leading to obesity

5.3 Adipokines and Hepcidin in obesity

Adipose tissue in patients with obesity can influence iron homeostasis by directly expressing hepcidin or regulating hepcidin expression through adipokines and pro-inflammatory cytokines [181, 182] (79, 89) **(**Fig. 7**)**. M1 macrophages, which increase in hypertrophic or dysfunctional adipose tissue in obesity, release leptin and other adipokines; which modulate hepcidin expression and impact, modulating hepcidin expression, and impact iron status [178]. Serum leptin levels are elevated in patients with obesity, and so are serum hepcidin levels [183]. Placing iron-overloaded leptin receptor-deficient (*db/db)* mice on HID decreased body weight, liver lipid droplets, and hepatic triglyceride levels [184]. Further, work with leptin-deficient (*ob/ob*) and (*db/db*) mice has demonstrated a marked reduction in serum hepcidin levels [185] through the IL-6/STAT3 signaling pathway [186]. Exposure of human hepatoma cells (HuH7) to leptin was reported to upregulate hepcidin mRNA expression, a response dampened by JAK2 inhibitors. Mutations in the STAT3 motif that binds the HAMP promoter were associated with reduced hepcidin promoter activity [187]. Recombinant leptin therapy has also been shown to restore hepcidin mRNA expression and serum hepcidin synthesis.

6 The gut Microbiome and the iron-lipid axis

Emerging evidence suggests that the gut microbiome helps shape the complex interplay between iron and lipid metabolism [188]. The gut microbiota, a key regulator of several metabolic pathways, is known to influence and be influenced by lipid metabolism [189]. This is further supported by the observation that diet composition significantly alters the gut microbiome architecture [190]. Moreover, HFD increases the *Firmicutes*-to-*Bacteroidetes* ratio, a marker of gut dysbiosis (reduced gut microbial diversity), especially in mice with obesity [191]. Major phyla of the gut microbiome, including *Firmicutes* and *Bacteroidetes* are particularly involved in regulating lipid metabolism in mammals [192]. Regarding iron, less than 10% of dietary iron is absorbed into the circulation; much of the remaining 90% is excreted in feces [193]. Gut resident microbes use unabsorbed iron for growth and virulence [194]. Therefore, ID and iron overload disrupt the gut microbiome architecture, leading to gut dysbiosis and inflammation [195]. Iron fortification in infants has been shown to alter gut microbiota composition by reducing beneficial *Bifidobacteria* levels and promoting the growth of *Escherichia coli* and other enteropathogenesis [196]. Gram-negative bacteria, including *E. coli*, *Shigella*, and *Salmonella* compete for unabsorbed dietary iron in the gut for growth and virulence. Iron overload has been linked to the development and progression of colorectal cancer [197]. These changes help shift the microbiome composition away from beneficial species like *Akkermansia*, *Bifidobacteria*, and *Lactobacillus* to pathogenic bacteria like *Romboutsia* and *Erysipelato clostridium* [198].

HID was reported to impair the structure of intestinal villi and microvilli and increase the production of inflammatory markers (IL-6, IL-1β, TNF-α, iNOS). HID was also reported to increase the abundance of inflammation-related bacterial species such as *Romboutsia* and *Erysipelatoclostridium* [199], *Clostridium difficile*, and *Clostridium perfringens* [200]. Populating the gut with beneficial bacteria like *Akkermansia muciniphila* was shown to correlate negatively with patients of obesity and diabetes and to protect against colitis [201]. Reduced prevalence of *Akkermansia* in hosts on HID suggests impaired intestinal barrier function [198]. *Bifidobacterium* and *Lactobacillus* species help maintain gut health and possibly reduce visceral fat and waist circumference in patients with obesity [202]. These observations notwithstanding, the fact remains that weight loss may relate more to altered expression of genes involved in adipogenesis and lipolysis or intestinal dysfunction than to dysbiosis [203] (134, 135) (Fig. 8).

The gut microbiota modulates dietary iron uptake predominantly through metabolic byproducts such as short-chain fatty acids (SCFAs) and microbial competition. Fermentation of dietary fibers by bacteria such as *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium* yields acetate, propionate, and butyrate [204]. SCFAs acidify the intestinal lumen, promoting conversion of dietary iron into its bioavailable Fe^{2+} form, which is more efficiently absorbed via enterocyte DMT1 and other transporters. Butyrate, in particular, enhances gut barrier integrity and supports tight-junction protein expression, minimizing inflammation-driven hepcidin synthesis in the liver, which otherwise downregulates iron export via FPN [205]. Concurrently, microbial taxa compete with the host for luminal iron through siderophore production, potentially reducing bioavailable iron for absorption. Additionally, certain gut bacteria express heme-degrading enzymes and influence local iron pools, affecting the balance between microbial uptake and host absorption.

Gut-derived SCFAs and bile acids exert significant regulatory influence on hepatic lipid synthesis, storage, and oxidation. Approximately 30–70% of SCFAs are absorbed into the portal circulation, with acetate serving as a substrate for hepatic lipogenesis and cholesterol synthesis, while propionate mitigates lipogenesis by inhibiting key enzymes and upregulating gluconeogenesis; butyrate modulates gene expression through histone deacetylase (HDAC) inhibition and G-protein–coupled receptor (GPCR) engagement, suppressing lipogenic factors such as PPARγ [204, 206–208]

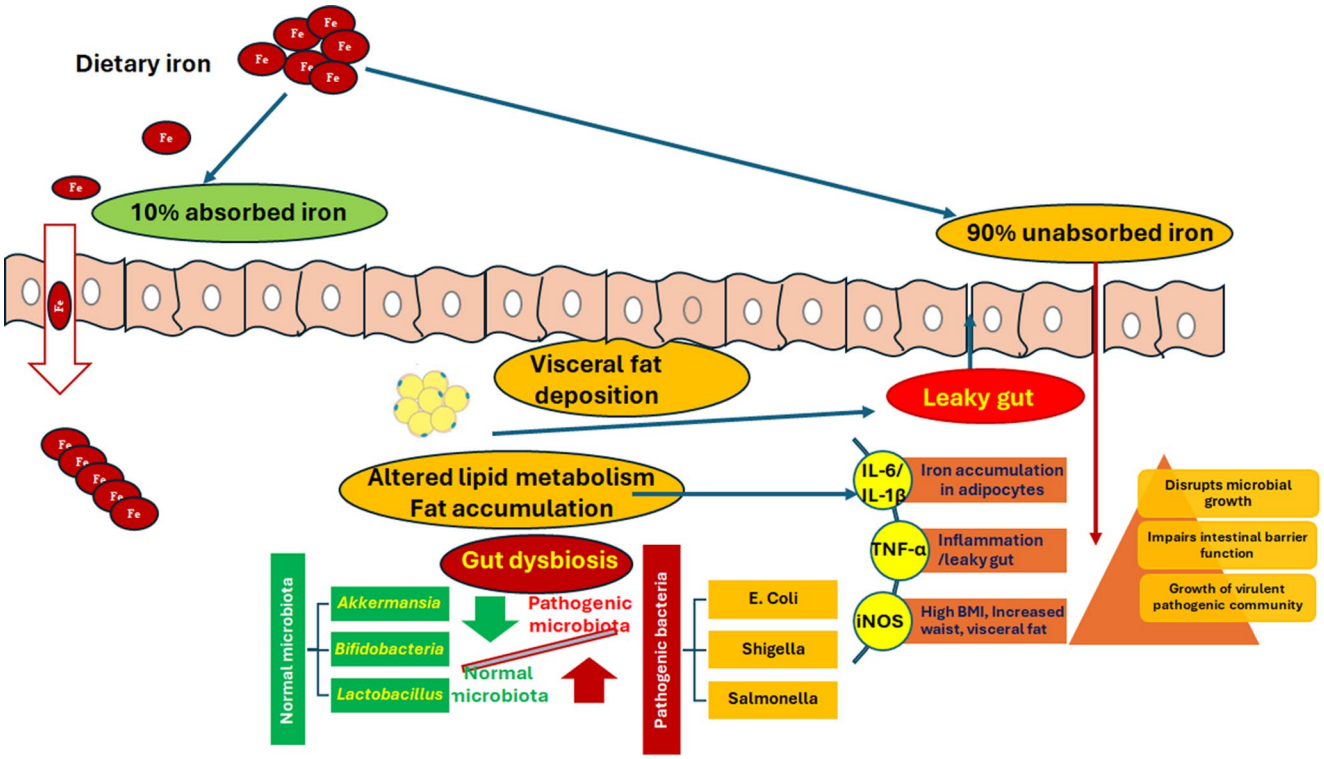


Fig. 8 Unabsorbed iron and HFD versus gut microbiota. Unabsorbed iron and HFD in the gastrointestinal tract foster the growth of pathogenic bacteria leading to gut microbiota dysbiosis, which triggers local inflammation that compromises the integrity of the intestinal epithelial barrier

SCFAs further activate receptors like free fatty acid receptor 2 (GPR43/FFA2) and GPR41/FFA3 in the liver and adipose tissue, reducing triglyceride storage and promoting β-oxidation via AMPK and PPARα pathways [209, 210]. Gut bacteria also deconjugate and 7α-dehydroxylate primary bile acids chenodeoxycholic acid (CDCA), and cholic acid (CA) into secondary bile acids such as deoxycholic acid (DCA) and lithocholic acid (LCA) via bile salt hydrolases (BSH) and bai operon enzymes (e.g., in *Clostridium scindens*) [207, 211]. These secondary bile acids engage farnesoid x receptor (FXR) and G-protein coupled bile receptor 1 (TGR5), nuclear and membrane receptors pivotal for lipid metabolism: FXR activation inhibits hepatic VLDL secretion and induces FGF19 to regulate lipogenesis and cholesterol homeostasis, while TGR5 improves energy expenditure and insulin sensitivity [209, 212]. Dysbiosis marked by altered bile acid profiles and reduced SCFA-producers leads to elevated gut permeability and LPS translocation, triggering hepatic inflammation via toll-like receptor 4 (TLR4) signaling that exacerbates steatosis and NAFLD progression. In short, the gut microbiota profoundly influences the iron–lipid–inflammation axis through the production of metabolites such as SCFAs and secondary bile acids, which regulate iron absorption, lipid metabolism, and immune responses. Hence targeted modulation of the microbiome, including the use of probiotics and next-generation microbial therapeutics, holds promise as a novel strategy to restore metabolic homeostasis and mitigate disorders like iron dysregulation and NAFLD.

7 Role of ferroptosis in obesity and metabolic disorders

Ferroptosis, an iron-dependent, lipid peroxidation-driven form of regulated cell death, has garnered attention for its potential involvement in metabolic regulation. While extensively characterized by cancer biology and neurodegeneration, its precise role in adipose tissue physiology remains incompletely defined. Recent studies provide intriguing evidence that ferroptotic signaling intersects with lipid metabolism, energy homeostasis, and obesity-related pathologies. A study exploring adipose tissue ferroptotic signatures in obesity reported a marked suppression of ferroptosis-associated pathways in both human and murine models of obesity. Pharmacological induction of ferroptotic signaling via sub-lethal doses of ferroptosis agonists attenuated lipid accumulation in cultured adipocytes and HFD-fed mice. Moreover, genetic manipulation enhancing ferroptotic activity either through adipocyte-specific overexpression of acyl-coenzyme A synthetase long-chain family member 4 (ACSL4) or deletion of

ferritin heavy chain (FTH1) conferred resistance to HFD-induced adipose expansion and metabolic derangements [213]. Importantly, mitochondrial iron overload exacerbates lipid peroxidation, contributing to ferroptosis [2]. Ferroptosis, an iron-dependent form of regulated cell death defined by lipid peroxidation, plays contrasting yet significant roles in adipose and hepatic tissues [214]. In adipose tissue, ferroptotic signaling is notably downregulated in obesity [213], contributing to excessive lipid deposition and impaired browning [215]; conversely, moderate activation of ferroptosis such as through adipocyte-specific overexpression of ACSL4 or deletion of ferritin heavy chain (Fth) has been shown to enhance thermogenesis via the HIF-1α–c-Myc–PGC-1β axis, thereby reducing adiposity and improving metabolic health [154, 216, 217]. In hepatic tissue, ferroptosis contributes to the progression of steatosis and metabolic dysfunction-associated steatohepatitis (MASH) [218]; in obese mouse models (e.g., ob/ob mice or MCD-fed), indicators of ferroptosis such as lipid peroxidation and glutathione peroxidase 4 (GPX4) depletion are prominent but can be reversed by ferroptosis inhibitors like ferrostatin-1 or liproxstatin-1 [219]. These interventions reduce oxidative stress, restore GPX4 levels, attenuate inflammation and fibrosis, and improve liver histology [214]. This evidence indicate a tissue-specific paradigm wherein activation of ferroptosis in adipose tissue promotes metabolic adaptation and counteracts obesity, while inhibition of ferroptosis in the liver confers protection against steatotic and inflammatory liver diseases. Mechanistically, these interventions activated a thermogenic program mediated via c-Myc and peroxisome proliferator-activated receptor gamma coactivator-1 beta (Pgc1β), facilitated by 5,15-dihydroxyeicosatetraenoic acid (5,15-DiHETE)-induced degradation of HIF1α [213]. Collectively, these findings position ferroptotic signaling as a potential modulator of adipose tissue plasticity and a therapeutic target against obesity.

Complementing these findings, natural bioactive compounds have been investigated for their anti-obesity effects mediated through ferroptosis modulation. Houttuynia cordata thunb and its active constituent sodium houttuybonate demonstrated efficacy in promoting the browning of inguinal white adipose tissue (iWAT) in HFD-induced obese mice. Sodium houttuybonate attenuated ferroptosis by upregulating GPX4, lowering malondialdehyde (MDA) levels, and enhancing antioxidant defenses such as superoxide dismutase (SOD). AMPK/NRF2/HMOX-1 axis underpinned these effects, while pharmacological inhibition of NRF2 abrogated sodium houttuybonate-mediated benefits. This suggests that sodium houttuybonate counteracts obesity by suppressing ferroptosis and stimulating thermogenic programs via the AMPK-NRF2-HMOX-1 pathway [220]. In hepatic metabolism, ferroptosis contributes significantly to obesity-related liver pathologies, including MASH. In ob/ob mice, ferroptotic hallmarks such as lipid peroxidation, ROS accumulation, and reduced GPX4 activity were prominent. Treatment with ferrostatin-1, a ferroptosis inhibitor, mitigated hepatic steatosis, normalized lipogenesis markers, reduced oxidative stress, alleviated iron overload, and reprogrammed macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotypes [219]. Additionally, ferrostatin restored mitochondrial function, underscoring its therapeutic promise for obesity-associated liver disorders. Similarly, metformin, a widely used for T2DM management, exhibits anti-ferroptotic properties in NAFLD. By activating AMPK, metformin stabilized FPN expression through inhibition of lysosomal degradation, alleviating hepatic iron overload and ferroptotic damage. These findings unveil an AMPK-FPN axis in metformin's hepatoprotective effects and highlight ferroptosis as a critical node in NAFLD progression [138]. These studies converge on ferroptosis as a pivotal mechanism linking iron metabolism, lipid peroxidation, and metabolic homeostasis. Both activation and inhibition of ferroptotic signaling demonstrate context-dependent therapeutic potential: ferroptosis induction in adipose tissue may promote browning and combat obesity, while ferroptosis inhibition in the liver may protect against steatosis and inflammation. Targeting ferroptosis with pharmacological agents or bioactive compounds represents an emerging strategy for addressing obesity and its associated metabolic complications, warranting further translational and clinical investigation.

8 Conclusion

The interplay between iron metabolism and obesity reveals a paradoxical relationship, as obesity is linked to both ID and iron overload, exacerbated by chronic inflammation that elevates hepcidin levels, inhibiting iron absorption and recycling, ultimately leading to functional ID despite high tissue iron stores, which worsens insulin resistance and metabolic dysfunction. Adipose tissue not only stores lipids but also influences iron metabolism through adipokines like leptin and adiponectin, where leptin modulates hepcidin synthesis and adiponectin enhances iron uptake during erythropoiesis, contributing to obesity-related metabolic disorders. Moreover, excess iron promotes oxidative stress and lipid peroxidation, key factors in hepatic inflammation and fibrosis in NAFLD, with iron overload exacerbating hepatic steatosis and disrupting lipid metabolism through increased

lipogenesis and very low-density lipoprotein (VLDL) secretion. Hepcidin, which regulates iron export via FPN, when dysregulated in obesity and NAFLD, leads to impaired iron distribution and hepatic iron accumulation, further driving oxidative stress and the progression from NAFLD to NASH. Elevated body iron levels in patients with obesity are associated with increased insulin resistance and a heightened risk of T2DM, while ID has been shown to improve glucose tolerance in animal models, highlighting the importance of maintaining iron balance for metabolic health. Iron also plays a crucial role in mitochondrial function and energy production, serving as a cofactor for enzymes in the TCA cycle and ETC, but iron dyshomeostasis can impair mitochondrial function, reduce energy expenditure and contributing to obesity. Furthermore, the gut microbiome significantly influences iron and lipid metabolism, with dysbiosis from HFD leading to inflammation and impaired iron absorption, while excessive iron can disrupt gut health, promoting pathogenic bacteria growth and inflammation. Therapeutically, modulating hepcidin levels offers a promising strategy for managing iron dysregulation in metabolic disorders, with hepcidin antagonists potentially mitigating inflammation-induced hypoferremia and iron supplementation improving mitochondrial function in iron-deficient individuals. This review emphasizes the need to understand the complex relationships between iron metabolism, lipid metabolism, and obesity, as disruptions in iron homeostasis play a critical role in metabolic disorders like in patients with diabetes, NAFLD, and insulin resistance, providing insights for targeted therapies to address obesity and related diseases while calling for further research into the molecular mechanisms of these interactions and the therapeutic potential of iron metabolism modulation.

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Declarations

Competing interests The authors declare no competing interests.

References

1. Rah B, Farhat NM, Hamad M, Muhammad JS. Jak/STAT signaling and cellular iron metabolism in hepatocellular carcinoma: therapeutic implications. Clin Exp Med. 2023;23(7):3147–57. https://doi.org/10.1007/s10238-023-01047-8.
2. Ru Q, Li Y, Chen L, Wu Y, Min J, Wang F. Iron homeostasis and ferroptosis in human diseases: mechanisms and therapeutic prospects. Sig Transduct Target Ther [Internet]. 2024 [cited 2025 Mar 14];9:1–64. Available from: https://www.nature.com/articles/s41392-024-01969-z
3. Wallace DF. The regulation of iron absorption and homeostasis. The Clinical Biochemist Reviews [Internet]. 2016 [cited 2024 Nov 25];37:51. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5198508/
4. Xu Y, Alfaro-Magallanes VM, Babitt JL. Physiological and pathophysiological mechanisms of hepcidin regulation: clinical implications for iron disorders. Br J Haematol. 2021;193:882–93. https://doi.org/10.1111/bjh.17252.
5. Gulec S, Anderson GJ, Collins JF. Mechanistic and regulatory aspects of intestinal iron absorption. Am J Physiol Gastrointest Liver Physiol [Internet]. 2014 [cited 2025 Mar 14];307:G397–409. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4137115/
6. Qiu F, Wu L, Yang G, Zhang C, Liu X, Sun X, et al. The role of iron metabolism in chronic diseases related to obesity. Mol Med. 2022;28:130. https://doi.org/10.1186/s10020-022-00558-6.
7. Deugnier Y, Bardou-Jacquet É, Lainé F. Dysmetabolic iron overload syndrome (DIOS). La Presse Médicale [Internet]. 2017 [cited 2024 Dec 3];46:e306–11. Available from: https://www.sciencedirect.com/science/article/pii/S075549821730458X?casa_token=eT9M-GyiEVgAAAAA:Aq8hyofHR_8Ly6hCbcY6SfXQ08Ma7PalPnfQdY3wvnoIHevOprHyYPRKICLl5I8dr50wQTCxjg
8. Murali AR, Gupta A, Brown K. Systematic review and meta-analysis to determine the impact of iron depletion in dysmetabolic iron overload syndrome and non-alcoholic fatty liver disease. Hepatology Research [Internet]. 2018 [cited 2024 Nov 26];48. Available from: https://onlinelibrary.wiley.com/doi/https://doi.org/10.1111/hepr.12921
9. Mohajan D, Mohajan HK. Obesity and its related diseases: a new escalating alarming in global health. Journal of Innovations in Medical Research [Internet]. 2023 [cited 2024 Dec 1];2:12–23. Available from: https://www.paradigmpress.org/jimr/article/view/505
10. Kovalic AJ, Cholankeril G, Satapathy SK. Nonalcoholic fatty liver disease and alcoholic liver disease: metabolic diseases with systemic manifestations. Translational Gastroenterology and Hepatology [Internet]. 2019 [cited 2024 Dec 1];4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6789306/
11. González-Domínguez Á, Visiedo-García FM, Domínguez-Riscart J, González-Domínguez R, Mateos RM, Lechuga-Sancho AM. Iron metabolism in obesity and metabolic syndrome. International journal of molecular sciences [Internet]. 2020 [cited 2024 Dec 1];21:5529. Available from: https://www.mdpi.com/1422-0067/21/15/5529
12. Oshaug A, Bugge KH, Bjønnes CH, Borch-Iohnsen B, Neslein IL. Associations between serum ferritin and cardiovascular risk factors in healthy young men. A cross sectional study. European journal of clinical nutrition [Internet]. 1995 [cited 2025 Feb 1];49:430–8. Available from: https://europepmc.org/article/med/7656886
13. Dongiovanni P, Ruscica M, Rametta R, Recalcati S, Steffani L, Gatti S et al. Dietary iron overload induces visceral adipose tissue insulin resistance. The American journal of pathology [Internet]. 2013 [cited 2024 Dec 3];182:2254–63. Available from: https://www.sciencedirect.com/science/article/pii/S0002944013001971

14. Valenti L, Remondini E, Fracanzani AL, Spada A, Colombo S, Guzzo A et al. Effect of iron depletion liver function and insulin resistance in patients with NASH and fatty liver. Hepatology [Internet]. 2005 [cited 2025 Feb 1];42:619A-619A. Available from: https://air.unimi.it/handle/2434/17286
15. Aigner E, Feldman A, Datz C. Obesity as an emerging risk factor for iron deficiency. Nutrients [Internet]. 2014 [cited 2024 Dec 2];6:3587–600. Available from: https://www.mdpi.com/2072-6643/6/9/3587
16. Paul BT, Manz DH, Torti FM, Torti SV. Mitochondria and iron: current questions. Expert Rev Hematol. 2017;10:65–79.
17. Cheng R, Dhorajia V, Kim J, Kim Y. Mitochondrial iron metabolism and neurodegenerative diseases. Neurotoxicology [Internet]. 2022 [cited 2025 Mar 14];88:88–101. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8748425/
18. Zong Y, Li H, Liao P, Chen L, Pan Y, Zheng Y et al. Mitochondrial dysfunction: mechanisms and advances in therapy. Sig Transduct Target Ther [Internet]. 2024 [cited 2025 Mar 14];9:1–29. Available from: https://www.nature.com/articles/s41392-024-01839-8
19. Creighton Mitchell T, McClain DA. Diabetes and hemochromatosis. Curr Diab Rep. 2014;14:488. https://doi.org/10.1007/s11892-014-0488-y.
20. Hamad M, Mohammed AK, Hachim MY, Mukhopadhy D, Khalique A, Laham A et al. Heme Oxygenase-1 (HMOX-1) and inhibitor of differentiation proteins (ID1, ID3) are key response mechanisms against iron-overload in pancreatic β-cells. Molecular and Cellular Endocrinology [Internet]. 2021 [cited 2025 Feb 2];538:111462. Available from: https://www.sciencedirect.com/science/article/pii/S0303720721003063?casa_token=1IAgf8Eg7joAAAAA:Wjpdcs2VWEm9vZjcqlrd315zR6hXjw9HSqwknaqUglmJrY6smXrsLxWdSgSDzraO0-yYMprnico
21. Simcox JA, McClain DA. Iron and diabetes risk. Cell Metab. 2013;17:329–41.
22. Harrison AV, Lorenzo FR, McClain DA. Iron and the pathophysiology of diabetes. Annu Rev Physiol. 2023;85:339–62. https://doi.org/10.1146/annurev-physiol-022522-102832.
23. Gabrielsen JS, Gao Y, Simcox JA, Huang J, Thorup D, Jones D et al. Adipocyte iron regulates adiponectin and insulin sensitivity. The Journal of clinical investigation [Internet]. 2012 [cited 2024 Nov 26];122:3529–40. Available from: https://www.jci.org/articles/view/44421
24. Citelli M, Fonte-Faria T, Nascimento-Silva V, Renovato-Martins M, Silva R, Luna AS, et al. Obesity promotes alterations in iron recycling. Nutrients. 2015;7:335–48.
25. Kerkadi A, Mohsen Ali R, Shehada AH, Abdelnasser AbouHassanein A, Moawad E, Bawadi J. Association between central obesity indices and iron status indicators among Qatari adults. PLoS ONE. 2021;16:e0250759.
26. Alshwaiyat N, Ahmad A, Wan Hassan WMR, Al–jamal H. Association between obesity and iron deficiency (Review). Exp Ther Med [Internet]. 2021 [cited 2024 Dec 2];22:1268. Available from: http://www.spandidos-publications.com/https://doi.org/10.3892/etm.2021.10703
27. Sanad M, Osman M, Gharib A. Obesity modulate serum hepcidin and treatment outcome of iron deficiency anemia in children: a case control study. Ital J Pediatr. 2011;37:34.
28. Kim SL, Shin S, Yang SJ. Iron homeostasis and energy metabolism in obesity. Clinical nutrition research [Internet]. 2022 [cited 2024 Dec 1];11:316. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9633967/
29. Rodríguez-Mortera R, Caccavello R, Hermo R, Garay-Sevilla ME, Gugliucci A. Higher Hepcidin Levels in Adolescents with Obesity Are Associated with Metabolic Syndrome Dyslipidemia and Visceral Fat. Antioxidants [Internet]. 2021 [cited 2025 Jul 19];10:751. Available from: https://www.mdpi.com/2076-3921/10/5/751.
30. Awoniyi A, Daniel O, Babatunde O. Dietary Iron Uptake and Absorption. 2024 [cited 2024 Dec 1]; Available from: https://www.intechopen.com/online-first/89440
31. Mleczko-Sanecka K, Silvestri L. Cell-type-specific insights into iron regulatory processes. Am J Hematol. 2021;96(1):110–27. https://doi.org/10.1002/ajh.26001.
32. Li C, Zhou L, Yin X. Pathophysiological aspects of transferrin-A potential nano-based drug delivery signaling molecule in therapeutic target for varied diseases. Frontiers in Pharmacology [Internet]. 2024 [cited 2024 Dec 1];15:1342181. Available from: https://www.frontiersin.org/articles/https://doi.org/10.3389/fphar.2024.1342181/full
33. Yang F, Zhang G, An N, Dai Q, Cho W, Shang H et al. Interplay of ferroptosis, cuproptosis, and PANoptosis in cancer treatment-induced cardiotoxicity: Mechanisms and therapeutic implications. Seminars in Cancer Biology [Internet]. Elsevier; 2024 [cited 2024 Dec 1]. Available from: https://www.sciencedirect.com/science/article/pii/S1044579X24000762?casa_token=PobKPuT0qdAAAAAA:NJki9F31oqwvksX5nt-fcyqoExXVx2qYBW9b-iFLR1INrCj9RfUQAHrspDADiX6XP6GzXedQLxg
34. Galy B, Conrad M, Muckenthaler M. Mechanisms controlling cellular and systemic iron homeostasis. Nature Reviews Molecular Cell Biology [Internet]. 2024 [cited 2024 Dec 1];25:133–55. Available from: https://www.nature.com/articles/s41580-023-00648-1
35. Mackenzie EL, Iwasaki K, Tsuji Y. Intracellular iron transport and storage: from molecular mechanisms to health implications. Antioxid Redox Signal. 2008;10:997–1030.
36. Sobieska K, Buczyńska A, Krętowski AJ, Popławska-Kita A. Iron homeostasis and insulin sensitivity: unraveling the complex interactions. Rev Endocr Metab Disord. 2024;25:925–39. https://doi.org/10.1007/s11154-024-09908-7.
37. Holgado AH, Gallego-Hernanz MP. Iron Metabolism: New Biomarkers Implicated. New Trends In Biomarkers and Diseases Research: An Overview [Internet]. Bentham Science Publishers; 2017 [cited 2025 Feb 2]. pp. 80–120. Available from: https://www.benthamdirect.com/content/books/9781681084954.chapter-4
38. Camaschella C, Girelli D. The changing landscape of iron deficiency. Mol Aspects Med. 2020;75:100861.
39. Pietrangelo A. Hepcidin in human iron disorders: therapeutic implications. Journal of Hepatology [Internet]. 2011 [cited 2024 Dec 1];54:173–81. Available from: https://www.sciencedirect.com/science/article/pii/S0168827810007300
40. Silva B, Faustino P. An overview of molecular basis of iron metabolism regulation and the associated pathologies. Biochimica et Biophysica Acta (BBA). 2015;1852:1347–59.
41. Katsarou A, Pantopoulos K. Hepcidin therapeutics. Pharmaceuticals. 2018;11:127.
42. Bajbouj K, Shafarin J, Allam H, Madkour M, Awadallah S, El-Serafy A et al. Elevated Levels of Estrogen Suppress Hepcidin Synthesis and Enhance Serum Iron Availability in Premenopausal Women. Exp Clin Endocrinol Diabetes [Internet]. 2018 [cited 2024 Jul 19];126:453–9. Available from: http://www.thieme-connect.de/DOI/DOI?10.1055/s-0043-124077
43. Yook J-S, Thomas SS, Toney AM, You M, Kim Y-C, Liu Z et al. Dietary iron deficiency modulates adipocyte iron homeostasis, adaptive thermogenesis, and obesity in C57BL/6 mice. The Journal of nutrition [Internet]. 2021 [cited 2024 Dec 1];151:2967–75. Available from: https://www.sciencedirect.com/science/article/pii/S0022316622003686
44. Muhammad JS, Bajbouj K, Shafarin J, Hamad M. Estrogen-induced epigenetic silencing of FTH1 and TFRC genes reduces liver cancer cell growth and survival. Epigenetics. 2020;15:1302–18.
45. Yanamadala V. Lipid Metabolism. Essential Medical Biochemistry and Metabolic Disease [Internet]. Cham: Springer Nature Switzerland; 2024 [cited 2025 Feb 2]. pp. 35–90. Available from: https://link.springer.com/https://doi.org/10.1007/978-3-031-59394-9_2

46. Grundy SM. What is the contribution of obesity to the metabolic syndrome? Endocrinology and Metabolism Clinics [Internet]. 2004 [cited 2025 Feb 2];33:267–82. Available from: https://www.endo.theclinics.com/article/S0889-8529(04)00018-0/abstract
47. Smith U. Abdominal obesity: a marker of ectopic fat accumulation. The Journal of clinical investigation [Internet]. 2015 [cited 2025 Feb 2];125:1790–2. Available from: https://www.jci.org/articles/view/81507
48. Shen X, Yu Z, Wei C, Hu C, Chen J. Iron metabolism and ferroptosis in nonalcoholic fatty liver disease: what is our next step? American Journal of Physiology-Endocrinology and Metabolism [Internet]. 2024 [cited 2025 Feb 2];326:E767–75. Available from: https://doi.org/10.1152/ajpendo.00260.2023
49. Lim S, Kim J-W, Targher G. Links between metabolic syndrome and metabolic dysfunction-associated fatty liver disease. Trends in Endocrinology & Metabolism [Internet]. 2021 [cited 2025 Feb 3];32:500–14. Available from: https://www.cell.com/trends/endocrinology-metabolism/fulltext/S1043-2760(21)00089-8?dgcid=raven_jbs_aip_email
50. Hsu CC, Senussi NH, Fertrin KY, Kowdley KV. Iron overload disorders. Hepatol Commun. 2022;6:1842–54. https://doi.org/10.1002/hep4.2012.
51. Chen Z, Tian R, She Z, Cai J, Li H. Role of oxidative stress in the pathogenesis of nonalcoholic fatty liver disease. Free Radical Biology and Medicine [Internet]. 2020 [cited 2025 Mar 15];152:116–41. Available from: https://www.sciencedirect.com/science/article/pii/S0891584919315151
52. Musso G, Gambino R, Cassader M. Non-alcoholic fatty liver disease from pathogenesis to management: an update. Obesity Reviews [Internet]. 2010 [cited 2025 Feb 3];11:430–45. Available from: https://onlinelibrary.wiley.com/doi/https://doi.org/10.1111/j.1467-789X.2009.00657.x
53. Giudetti AM. Lipid metabolism in obesity [Internet]. Frontiers in Physiology. Frontiers Media SA; 2023 [cited 2025 Feb 3]. p. 1268288. Available from: https://www.frontiersin.org/articles/https://doi.org/10.3389/fphys.2023.1268288/full
54. Rockfield S, Chhabra R, Robertson M, Rehman N, Bisht R, Nanjundan M. Links between iron and lipids: implications in some major human diseases. Pharmaceuticals [Internet]. 2018 [cited 2025 Feb 3];11:113. Available from: https://www.mdpi.com/1424-8247/11/4/113
55. Ahmed U, Latham PS, Oates PS. Interactions between hepatic iron and lipid metabolism with possible relevance to steatohepatitis. World journal of gastroenterology: WJG [Internet]. 2012 [cited 2025 Feb 3];18:4651. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3442203/
56. Yang X, Wang X, Yang Z, Lu H. Iron-mediated regulation in adipose tissue: a comprehensive review of metabolism and physiological effects. Curr Obes Rep. 2025;14:4. https://doi.org/10.1007/s13679-024-00600-0.
57. Pietrangelo A. Hereditary hemochromatosis — a new look at an old disease. N Engl J Med. 2004;350:2383–97. https://doi.org/10.1056/NEJMra031573.
58. Hilton C, Sabaratnam R, Drakesmith H, Karpe F. Iron, glucose and fat metabolism and obesity: an intertwined relationship. International Journal of Obesity [Internet]. 2023 [cited 2024 Dec 2];47:554–63. Available from: https://www.nature.com/articles/s41366-023-01299-0
59. Stoffel NU, El-Mallah C, Herter-Aeberli I, Bissani N, Wehbe N, Obeid O et al. The effect of central obesity on inflammation, hepcidin, and iron metabolism in young women. International Journal of Obesity [Internet]. 2020 [cited 2024 Dec 2];44:1291–300. Available from: https://www.nature.com/articles/s41366-020-0522-x
60. Szrok-Jurga S, Czumaj A, Turyn J, Hebanowska A, Swierczynski J, Sledzinski T et al. The physiological and pathological role of acyl-coA oxidation. International Journal of Molecular Sciences [Internet]. 2023 [cited 2024 Dec 2];24:14857. Available from: https://www.mdpi.com/1422-0067/24/19/14857
61. Mailloux RJ. Teaching the fundamentals of electron transfer reactions in mitochondria and the production and detection of reactive oxygen species. Redox biology [Internet]. 2015 [cited 2024 Dec 2];4:381–98. Available from: https://www.sciencedirect.com/science/article/pii/S2213231715000178
62. Zhao R-Z, Jiang S, Zhang L, Yu Z-B. Mitochondrial electron transport chain, ROS generation and uncoupling. International journal of molecular medicine [Internet]. 2019 [cited 2024 Dec 2];44:3–15. Available from: https://www.spandidos-publications.com/ijmm/44/1/3
63. Buse G. Cytochrome c oxidase. Copper Proteins and Copper Enzymes [Internet]. CRC Press; 2018 [cited 2024 Dec 2]. pp. 119–50. Available from: https://www.taylorfrancis.com/chapters/edit/10.1201/9781351070898-4/cytochrome-oxidase-buse
64. Isaya G. Mitochondrial iron-sulfur cluster dysfunction in neurodegenerative disease. Front Pharmacol. 2014;5:29.
65. Martelli A, Puccio H. Dysregulation of cellular iron metabolism in Friedreich ataxia: from primary iron-sulfur cluster deficit to mitochondrial iron accumulation. Front Pharmacol [Internet]. 2014 [cited 2025 Jul 19];5. Available from: https://www.frontiersin.org/journals/pharmacology/articles/https://doi.org/10.3389/fphar.2014.00130/full
66. Gao J, Zhou Q, Wu D, Chen L. Mitochondrial iron metabolism and its role in diseases. Clin Chim Acta. 2021;513:6–12.
67. Yan F, Li K, Xing W, Dong M, Yi M, Zhang H. Role of iron-related oxidative stress and mitochondrial dysfunction in cardiovascular diseases. Oxid Med Cell Longev. 2022;2022:5124553.
68. Sawicki KT, De Jesus A, Ardehali H. Iron metabolism in cardiovascular disease: physiology, mechanisms, and therapeutic targets. Circ Res. 2023;132:379–96.
69. Pondarré C, Antiochos BB, Campagna DR, Clarke SL, Greer EL, Deck KM, et al. The mitochondrial ATP-binding cassette transporter Abcb7 is essential in mice and participates in cytosolic iron–sulfur cluster biogenesis. Hum Mol Genet. 2006;15:953–64.
70. Mena NP, Urrutia PJ, Lourido F, Carrasco CM, Núñez MT. Mitochondrial iron homeostasis and its dysfunctions in neurodegenerative disorders. Mitochondrion. 2015;21:92–105.
71. Zhao Y, Yang M, Liang X. The role of mitochondria in iron overload-induced damage. J Transl Med. 2024;22:1057.
72. Rineau E, Gueguen N, Procaccio V, Geneviève F, Reynier P, Henrion D et al. Iron deficiency without anemia decreases physical endurance and mitochondrial complex I activity of oxidative skeletal muscle in the mouse. Nutrients [Internet]. 2021 [cited 2024 Dec 2];13:1056. Available from: https://www.mdpi.com/2072-6643/13/4/1056
73. Imam MU, Zhang S, Ma J, Wang H, Wang F. Antioxidants mediate both iron homeostasis and oxidative stress. Nutrients. 2017;9:671.
74. Kitamura N, Yokoyama Y, Taoka H, Nagano U, Hosoda S, Taworntawat T et al. Iron supplementation regulates the progression of high fat diet induced obesity and hepatic steatosis via mitochondrial signaling pathways. Scientific reports [Internet]. 2021 [cited 2024 Dec 2];11:10753. Available from: https://www.nature.com/articles/s41598-021-89673-8
75. Swenson SA, Moore CM, Marcero JR, Medlock AE, Reddi AR, Khalimonchuk O. From synthesis to utilization: The ins and outs of mitochondrial heme. Cells [Internet]. 2020 [cited 2024 Dec 2];9:579. Available from: https://www.mdpi.com/2073-4409/9/3/579

76. Badenhorst CE, Goto K, O'Brien WJ, Sims S. Iron status in athletic females, a shift in perspective on an old paradigm. Journal of Sports Sciences [Internet]. 2021 [cited 2025 Feb 3];39:1565–75. Available from: https://www.tandfonline.com/doi/full/https://doi.org/10.1080/02640414.2021.1885782
77. Peyssonnaux C, Zinkernagel AS, Schuepbach RA, Rankin E, Vaulont S, Haase VH et al. Regulation of iron homeostasis by the hypoxia-inducible transcription factors (HIFs). The Journal of clinical investigation [Internet]. 2007 [cited 2024 Jul 19];117:1926–32. Available from: https://www.jci.org/articles/view/31370
78. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest. 2004;113:1271–6.
79. Millonig G, Ganzleben I, Peccerella T, Casanovas G, Brodziak-Jarosz L, Breitkopf-Heinlein K, et al. Sustained submicromolar H2O2 levels induce Hepcidin via signal transducer and activator of transcription 3 (STAT3). J Biol Chem. 2012;287:37472–82.
80. Andrews NC. Forging a field: the golden age of iron biology. Blood. 2008;112:219–30.
81. Hentze MW, Muckenthaler MU, Andrews NC. Balancing Acts: Molecular Control of Mammalian Iron Metabolism. Cell [Internet]. 2004 [cited 2025 Jul 19];117:285–97. Available from: https://www.cell.com/cell/abstract/S0092-8674(04)00343-5
82. Moreno-Navarrete JM, Ortega F, Moreno M, Ricart W, Fernández-Real JM. Fine-tuned iron availability is essential to achieve optimal adipocyte differentiation and mitochondrial biogenesis. Diabetologia. 2014;57:1957–67.
83. Moreno M, Ortega F, Xifra G, Ricart W, Fernández-Real JM, Moreno-Navarrete JM. Cytosolic aconitase activity sustains adipogenic capacity of adipose tissue connecting iron metabolism and adipogenesis. FASEB J. 2015;29:1529–39.
84. Moreno-Navarrete JM, Ortega F, Rodríguez A, Latorre J, Becerril S, Sabater-Masdeu M, et al. *HMOX1* as a marker of iron excess-induced adipose tissue dysfunction, affecting glucose uptake and respiratory capacity in human adipocytes. Diabetologia. 2017;60:915–26.
85. Suzuki T, Komatsu T, Shibata H, Tanioka A, Vargas D, Kawabata-Iwakawa R, et al. Crucial role of iron in epigenetic rewriting during adipocyte differentiation mediated by JMJD1A and TET2 activity. Nucleic Acids Res. 2023;51:6120–42.
86. Oliveras-Cañellas N, Latorre J, Santos-González E, Lluch A, Ortega F, Mayneris-Perxachs J, et al. Inflammatory response to bacterial lipopolysaccharide drives iron accumulation in human adipocytes. Biomed Pharmacother. 2023;166:115428.
87. Trayhurn P, Origins. and early development of the concept that brown adipose tissue thermogenesis is linked to energy balance and obesity. Biochimie [Internet]. 2017 [cited 2024 Dec 2];134:62–70. Available from: https://www.sciencedirect.com/science/article/pii/S0300908416301742?casa_token=QmETGS1_mQ4AAAAA:oirnFFRnYdmjcLZRatSexGFmIzWnhJthK22H02_XjYXMGOEtb3T0-b5WEVIWDznZJfmVbjQQVL0
88. Ma W, Jia L, Xiong Q, Feng Y, Du H. The role of iron homeostasis in adipocyte metabolism. Food & function [Internet]. 2021 [cited 2024 Dec 2];12:4246–53. Available from: https://pubs.rsc.org/en/content/articlehtml/2021/xx/d0fo03442h
89. Takeda Y, Harada Y, Yoshikawa T, Dai P. Mitochondrial energy metabolism in the regulation of thermogenic brown fats and human metabolic diseases. International Journal of Molecular Sciences [Internet]. 2023 [cited 2024 Dec 2];24:1352. Available from: https://www.mdpi.com/1422-0067/24/2/1352
90. Bartelt A, Widenmaier SB, Schlein C, Johann K, Goncalves RL, Eguchi K et al. Brown adipose tissue thermogenic adaptation requires Nrf1-mediated proteasomal activity. Nature medicine [Internet]. 2018 [cited 2024 Dec 2];24:292–303. Available from: https://www.nature.com/articles/nm.4481
91. Tajima K, Ikeda K, Chang H-Y, Chang C-H, Yoneshiro T, Oguri Y et al. Mitochondrial lipoylation integrates age-associated decline in brown fat thermogenesis. Nature metabolism [Internet]. 2019 [cited 2024 Dec 2];1:886–98. Available from: https://www.nature.com/articles/s42255-019-0106-z
92. Petronek MS, Spitz DR, Allen BG. Iron–sulfur cluster biogenesis as a critical target in cancer. Antioxidants [Internet]. 2021 [cited 2024 Dec 2];10:1458. Available from: https://www.mdpi.com/2076-3921/10/9/1458
93. Singh AK. Understanding the Relationship between Iron and Lipid Metabolism in Non-alcoholic Fatty Liver Disease [Internet] [PhD Thesis]. Curtin University; 2022 [cited 2024 Dec 2]. Available from: https://espace.curtin.edu.au/handle/20.500.11937/93623
94. Deschemin J-C, Ransy C, Bouillaud F, Chung S, Galy B, Peyssonnaux C, et al. Hepcidin deficiency in mice impairs white adipose tissue browning possibly due to a defect in de novo adipogenesis. Sci Rep. 2023;13:12794.
95. Yook J-S, You M, Kim J, Toney AM, Fan R, Puniya BL, et al. Essential role of systemic iron mobilization and redistribution for adaptive thermogenesis through HIF2-α/hepcidin axis. Proc Natl Acad Sci U S A. 2021;118:e2109186118.
96. Sponton CH, de Lima-Junior JC, Leiria LO. What puts the heat on thermogenic fat: metabolism of fuel substrates. Trends in Endocrinology & Metabolism [Internet]. 2022 [cited 2024 Dec 2];33:587–99. Available from: https://www.cell.com/trends/endocrinology-metabolism/fulltext/S1043-2760(22)00100-X?dgcid=raven_jbs_etoc_email
97. Chernogubova E, Cannon B, Bengtsson T. Norepinephrine increases glucose transport in brown adipocytes via β3-adrenoceptors through a cAMP, PKA, and PI3-kinase-dependent pathway stimulating conventional and novel PKCs. Endocrinology [Internet]. 2004 [cited 2024 Dec 2];145:269–80. Available from: https://academic.oup.com/endo/article-abstract/145/1/269/2878243
98. Zhang Z, Yang D, Xiang J, Zhou J, Cao H, Che Q et al. Non-shivering thermogenesis signalling regulation and potential therapeutic applications of brown adipose tissue. International journal of biological sciences [Internet]. 2021 [cited 2024 Dec 2];17:2853. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8326120/
99. Yook J-S, You M, Kim Y, Zhou M, Liu Z, Kim Y-C et al. The thermogenic characteristics of adipocytes are dependent on the regulation of iron homeostasis. Journal of Biological Chemistry [Internet]. 2021 [cited 2024 Dec 2];296. Available from: https://www.jbc.org/article/S0021-9258(21)00225-8/abstract
100. Joffin N, Gliniak CM, Funcke J-B, Paschoal VA, Crewe C, Chen S, et al. Adipose tissue macrophages exert systemic metabolic control by manipulating local iron concentrations. Nat Metab. 2022;4:1474–94.
101. Ameka MK, Beavers WN, Shaver CM, Ware LB, Kerchberger VE, Schoenfelt KQ, et al. An iron refractory phenotype in obese adipose tissue macrophages leads to adipocyte iron overload. Int J Mol Sci. 2022;23:7417.
102. Ikeda Y, Watanabe H, Shiuchi T, Hamano H, Horinouchi Y, Imanishi M, et al. Deletion of H-ferritin in macrophages alleviates obesity and diabetes induced by high-fat diet in mice. Diabetologia. 2020;63:1588–602.
103. Zhang Z, Funcke J-B, Zi Z, Zhao S, Straub LG, Zhu Y, et al. Adipocyte iron levels impinge on a fat-gut crosstalk to regulate intestinal lipid absorption and mediate protection from obesity. Cell Metab. 2021;33:1624–e16399.

104. Hubler MJ, Erikson KM, Kennedy AJ, Hasty AH. Mfehi adipose tissue macrophages compensate for tissue iron perturbations in mice. Am J Physiol Cell Physiol. 2018;315:C319–29.
105. Yang Q, Jian J, Katz S, Abramson SB, Huang X. 17β-estradiol inhibits iron hormone hepcidin through an estrogen responsive element half-site. Endocrinology. 2012;153(7):3170–8.
106. Ikeda Y, Tajima S, Izawa-Ishizawa Y, Kihira Y, Ishizawa K, Tomita S, et al. Estrogen regulates Hepcidin expression via GPR30-BMP6-dependent signaling in hepatocytes. PLoS ONE. 2012;7:e40465.
107. Hamad M, Bajbouj K, Taneera J. The case for an estrogen-iron axis in health and disease. Exp Clin Endocrinol Diabetes. 2020;128:270–7.
108. Hou Y, Zhang S, Wang L, Li J, Qu G, He J et al. Estrogen regulates iron homeostasis through governing hepatic hepcidin expression via an estrogen response element. Gene [Internet]. 2012 [cited 2024 Jul 20];511:398–403. Available from: https://www.sciencedirect.com/science/article/pii/S0378111912011699?casa_token=mbqngUGVTFAAAAAA:ounrngMp9KrIKa4T68pPDWOoKR7M--rSI0pw-nkMEMsWLV21Cl9Ugt7IO706S2yzhnjGuD93pSY
109. Ahanchi NS, Khatami F, Llanaj E, Quezada-Pinedo HG, Dizdari H, Bano A, et al. The complementary roles of iron and estrogen in menopausal differences in cardiometabolic outcomes. Clin Nutr. 2024;43:1136–50.
110. Matta RA, AbdElftah ME, Essawy MG, Saedii AA. Interplay of serum hepcidin with female sex hormones, metabolic syndrome, and abdominal fat distribution among premenopausal and postmenopausal women. The Egyptian Journal of Internal Medicine [Internet]. 2022 [cited 2025 Jul 19];34:undefined-undefined. Available from: https://www.mendeley.com/catalogue/70b6b68c-a4b3-3d29-bf13-0c97307afbb1/.
111. Harrison-Findik DD. Gender-related variations in iron metabolism and liver diseases. World journal of hepatology [Internet]. 2010 [cited 2024 Jul 19];2:302. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2999297/
112. Park CY, Chung J, Koo K-O, Kim MS, Han SN. Hepatic iron storage is related to body adiposity and hepatic inflammation. Nutr Metab (Lond). 2017;14:14. https://doi.org/10.1186/s12986-017-0169-3.
113. Wylenzek F, Bühling KJ, Laakmann E. A systematic review on the impact of nutrition and possible supplementation on the deficiency of vitamin complexes, iron, omega-3-fatty acids, and lycopene in relation to increased morbidity in women after menopause. Arch Gynecol Obstet. 2024;310:2235–45.
114. Gozzelino R, Arosio P. Iron homeostasis in health and disease. Int J Mol Sci. 2016;17:130.
115. Lainé F, Ruivard M, Loustaud-Ratti V, Bonnet F, Calès P, Bardou-Jacquet E et al. Metabolic and hepatic effects of bloodletting in dysmetabolic iron overload syndrome: A randomized controlled study in 274 patients. Hepatology [Internet]. 2017 [cited 2025 Feb 3];65:465–74. Available from: https://journals.lww.com/01515467-201702000-00010
116. Teng I, Tseng S, Aulia B, Shih C, Bai C, Chang J. Can diet-induced weight loss improve iron homoeostasis in patients with obesity: a systematic review and meta-analysis. Obes Rev. 2020;21:e13080. https://doi.org/10.1111/obr.13080.
117. Lee HS, Park E. Association of serum ferritin level and depression with respect to the body mass index in Korean male adults. Nutrition Research and Practice [Internet]. 2019 [cited 2024 Dec 2];13:263–7. Available from: https://synapse.koreamed.org/articles/1125391
118. Britton L, Jaskowski L-A, Bridle K, Secondes E, Wallace D, Santrampurwala N, et al. Ferroportin expression in adipocytes does not contribute to iron homeostasis or metabolic responses to a high calorie diet. Cell Mol Gastroenterol Hepatol. 2018;5:319–31.
119. Liu L, Yan F, Yan H, Wang Z. Impact of iron supplementation on gestational diabetes mellitus: a literature review. Diabetes Obes Metab. 2023;25(2):342–53. https://doi.org/10.1111/dom.14886.
120. Garcia-Valdes L, Campoy C, Hayes H, Florido J, Rusanova I, Miranda MT et al. The impact of maternal obesity on iron status, placental transferrin receptor expression and hepcidin expression in human pregnancy. International journal of obesity [Internet]. 2015 [cited 2024 Dec 2];39:571–8. Available from: https://www.nature.com/articles/ijo20153
121. Gasmi A, Bjørklund G, Mujawdiya PK, Semenova Y, Peana M, Dosa A, et al. Micronutrients deficiences in patients after bariatric surgery. Eur J Nutr. 2022;61:55–67. https://doi.org/10.1007/s00394-021-02619-8.
122. Vaquero MP, Martínez-Suárez M, García-Quismondo Á, Del Cañizo FJ, Sánchez-Muniz FJ. Diabesity negatively affects transferrin saturation and iron status. The DICARIVA study. Diabetes Research and Clinical Practice [Internet]. 2021 [cited 2024 Dec 2];172:108653. Available from: https://www.sciencedirect.com/science/article/pii/S0168822721000061?casa_token=uCBqWujUA0wAAAAA:e49UxrouOz8m4DkGey5tBdXjtmH6x8076zZlxYFHFTlVCt_-xvx3rBbU1FLKg9TYt5FUkSwD6g
123. Laudisio D, de Alteriis G, Vetrani C, Aprano S, Pugliese G, Zumbolo F et al. Iron Levels and Markers of Inflammation in a Population of Adults with Severe Obesity, a Cross-Sectional Study. Nutrients [Internet]. 2023 [cited 2024 Dec 2];15:4702. Available from: https://www.mdpi.com/2072-6643/15/21/4702
124. Winter WE, Bazydlo LA, Harris NS. The molecular biology of human iron metabolism. Lab Med. 2014;45:92–102.
125. Fujii T, Asai T, Matsuo T, Okamura K. Effect of resistance exercise on iron status in moderately iron-deficient rats. Biol Trace Elem Res. 2011;144:983–91. https://doi.org/10.1007/s12011-011-9072-3.
126. Krisai P, Leib S, Aeschbacher S, Kofler T, Assadian M, Maseli A et al. Relationships of iron metabolism with insulin resistance and glucose levels in young and healthy adults. European journal of internal medicine [Internet]. 2016 [cited 2025 Feb 4];32:31–7. Available from: https://www.sciencedirect.com/science/article/pii/S0953620516300371
127. Nemeth E, Ganz T. Anemia of inflammation. Hematol Oncol Clin North Am. 2014;28:671–81. vi.
128. Dongiovanni P, Fracanzani AL, Fargion S, Valenti L. Iron in fatty liver and in the metabolic syndrome: a promising therapeutic target. J Hepatol. 2011;55:920–32.
129. Britton LJ, Subramaniam VN, Crawford DH. Iron and non-alcoholic fatty liver disease. World journal of gastroenterology [Internet]. 2016 [cited 2024 Dec 3];22:8112. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5037080/
130. Fernández-Real JM, Peñarroja G, Castro A, García-Bragado F, Hernández-Aguado I, Ricart W. Blood letting in high-ferritin type 2 diabetes: effects on insulin sensitivity and beta-cell function. Diabetes. 2002;51:1000–4.
131. Darshan D, Anderson G-J. Liver-gut axis in the regulation of iron homeostasis. World J Gastroenterol. 2007;13:4737–45.
132. Skikne BS, Punnonen K, Caldron PH, Bennett MT, Rehu M, Gasior GH, et al. Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: a prospective multicenter evaluation of soluble transferrin receptor and the sTfR/log ferritin index. Am J Hematol. 2011;86(11):923–7. https://doi.org/10.1002/ajh.22108.
133. Casu C, Nemeth E, Rivella S. Hepcidin agonists as therapeutic tools. Blood. 2018;131:1790–4. https://doi.org/10.1182/blood-2017-11-737411.
134. Blanchette NL, Manz DH, Torti FM, Torti SV. Modulation of hepcidin to treat iron deregulation: potential clinical applications. Expert Rev Hematol. 2016;9(2):169–86. https://doi.org/10.1586/17474086.2016.1124757.

135. Sebastiani G, Wilkinson N, Pantopoulos K. Pharmacological targeting of the Hepcidin/Ferroportin axis. Front Pharmacol. 2016;7:160.
136. Li L, Wang K, Jia R, Xie J, Ma L, Hao Z, et al. Ferroportin-dependent ferroptosis induced by ellagic acid retards liver fibrosis by impairing the SNARE complexes formation. Redox Biol. 2022;56:102435.
137. Zhang D-L, Rouault TA. How does hepcidin hinder ferroportin activity? Blood. 2018;131:840–2. https://doi.org/10.1182/blood-2018-01-824151.
138. Yue F, Shi Y, Wu S, Xing L, He D, Wei L, et al. Metformin alleviates hepatic iron overload and ferroptosis through AMPK-ferroportin pathway in HFD-induced NAFLD. iScience. 2023;26:108560.
139. Nemeth E, Ganz T. Hepcidin and Iron in Health and Disease. Annu Rev Med [Internet]. 2023 [cited 2025 Apr 17];74:261–77. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9943683/
140. Lehmann EF, Liziczai M, Drożdżyk K, Altermatt P, Langini C, Manolova V, et al. Structures of Ferroportin in complex with its specific inhibitor Vamifeport. Elife. 2023;12:e83053.
141. Traeger L, Wiegand SB, Sauer AJ, Corman BHP, Peneyra KM, Wunderer F, et al. UBA6 and NDFIP1 regulate the degradation of Ferroportin. Haematologica. 2022;107:478–88.
142. Miranda MA, St Pierre CL, Macias-Velasco JF, Nguyen HA, Schmidt H, Agnello LT et al. Dietary iron interacts with genetic background to influence glucose homeostasis. Nutrition & Metabolism [Internet]. 2019 [cited 2025 Jul 19];16:13. Available from: https://doi.org/10.1186/s12986-019-0339-6
143. Wang R, Liu Y, Thabane L, Olier I, Li L, Ortega-Martorell S, et al. Relationship between trajectories of dietary iron intake and risk of type 2 diabetes mellitus: evidence from a prospective cohort study. Nutr J. 2024;23:15.
144. Littlejohn PT, Bar-Yoseph H, Edwards K, Li H, Ramirez-Contreras CY, Holani R, et al. Multiple micronutrient deficiencies alter energy metabolism in host and gut microbiome in an early-life murine model. Front Nutr. 2023;10:1151670.
145. Rinaldi L, Pafundi PC, Galiero R, Caturano A, Morone MV, Silvestri C et al. Mechanisms of non-alcoholic fatty liver disease in the metabolic syndrome. A narrative review. Antioxidants [Internet]. 2021 [cited 2024 Dec 3];10:270. Available from: https://www.mdpi.com/2076-3921/10/2/270
146. Lian C-Y, Zhai Z-Z, Li Z-F, Wang L. High fat diet-triggered non-alcoholic fatty liver disease: A review of proposed mechanisms. Chemico-biological interactions [Internet]. 2020 [cited 2024 Dec 3];330:109199. Available from: https://www.sciencedirect.com/science/article/pii/S0009279720309030?casa_token=3Phgb6cyTNIAAAAA:-VOcQuahYYJ5wbJY1FXBZ945jZuE4B4adSG5rl3dkuQfZVFwm3B06LtB0-21-Uivz22uzxgiYg
147. Kouroumalis E, Tsomidis I, Voumvouraki A. Iron as a therapeutic target in chronic liver disease. World Journal of Gastroenterology [Internet]. 2023 [cited 2024 Dec 3];29:616. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9896614/
148. Barbalho SM, Laurindo LF, Tofano RJ, Flato UAP, Mendes CG, de Alvares Goulart R et al. Dysmetabolic iron overload syndrome: Going beyond the traditional risk factors associated with metabolic syndrome. Endocrines [Internet]. 2023 [cited 2024 Dec 3];4:18–37. Available from: https://www.mdpi.com/2673-396X/4/1/2
149. Li L-X, Guo F-F, Liu H, Zeng T. Iron overload in alcoholic liver disease: underlying mechanisms, detrimental effects, and potential therapeutic targets. Cell Mol Life Sci. 2022;79(4):201. https://doi.org/10.1007/s00018-022-04239-9.
150. Liu Y, Li G, Lu F, Guo Z, Cai S, Huo T. Excess iron intake induced liver injury: The role of gut-liver axis and therapeutic potential. Biomedicine & Pharmacotherapy [Internet]. 2023 [cited 2024 Dec 3];168:115728. Available from: https://www.sciencedirect.com/science/article/pii/S0753332223015263
151. Bloomer SA, Brown KE. Iron-induced liver injury: a critical reappraisal. International journal of molecular sciences [Internet]. 2019 [cited 2024 Dec 3];20:2132. Available from: https://www.mdpi.com/1422-0067/20/9/2132
152. Unruh D, Srinivasan R, Benson T, Haigh S, Coyle D, Batra N, et al. Red blood cell dysfunction induced by high-fat diet: potential implications for obesity-related atherosclerosis. Circulation. 2015;132(20):1898–908. https://doi.org/10.1161/CIRCULATIONAHA.115.017313.
153. Videla LA, Valenzuela R. Perspectives in liver redox imbalance: toxicological and pharmacological aspects underlying iron overloading, nonalcoholic fatty liver disease, and thyroid hormone action. Biofactors. 2022;48(2):400–15. https://doi.org/10.1002/biof.1797.
154. Yuan X, Li L, Zhang Y, Ai R, Li D, Dou Y, et al. Heme oxygenase 1 alleviates nonalcoholic steatohepatitis by suppressing hepatic ferroptosis. Lipids Health Dis. 2023;22:99. https://doi.org/10.1186/s12944-023-01855-7.
155. Alam S, Hasan MK, Neaz S, Hussain N, Hossain MF, Rahman T. Diabetes Mellitus: insights from epidemiology, biochemistry, risk factors, diagnosis, complications and comprehensive management. Diabetology [Internet]. 2021 [cited 2024 Dec 3];2:36–50. Available from: https://www.mdpi.com/2673-4540/2/2/4
156. Yameny AA, Diabetes Mellitus O. 2024. Journal of Bioscience and Applied Research [Internet]. 2024 [cited 2024 Dec 3];10:641–5. Available from: https://jbaar.journals.ekb.eg/article_382794.html
157. Wolide AD, Zawdie B, Alemayehu Nigatu T, Tadesse S. Evaluation of serum ferritin and some metal elements in type 2 diabetes mellitus patients: comparative cross-sectional study. DMSO [Internet]. 2016 [cited 2025 Feb 4];Volume 9:417–24. Available from: https://www.dovepress.com/evaluation-of-serum-ferritin-and-some-metal-elements-in-type-2-diabete-peer-reviewed-article-DMSO
158. Żekanowska E, Boinska J, Giemza-Kucharska P, Kwapisz J. Obesity and iron metabolism. BioTechnologia [Internet]. 2011 [cited 2025 Feb 4];92:147–52. Available from: https://www.termedia.pl/Journal/-85/pdf-23862-10?filename=06.pdf
159. Henriksen EJ, Diamond-Stanic MK, Marchionne EM. Oxidative stress and the etiology of insulin resistance and type 2 diabetes. Free Radical Biology and Medicine [Internet]. 2011 [cited 2025 Feb 4];51:993–9. Available from: https://www.sciencedirect.com/science/article/pii/S0891584910014103
160. Backe MB, Moen IW, Ellervik C, Hansen JB, Mandrup-Poulsen T. Iron regulation of pancreatic beta-cell functions and oxidative stress. Annu Rev Nutr. 2016;36:241–73. https://doi.org/10.1146/annurev-nutr-071715-050939.
161. Kataria Y, Wu Y, Horskjær P, de H, Mandrup-Poulsen T, Ellervik C. Iron status and gestational diabetes—a meta-analysis. Nutrients [Internet]. 2018 [cited 2024 Dec 3];10:621. Available from: https://www.mdpi.com/2072-6643/10/5/621
162. Holendová B, Stokičová L, Plecitá-Hlavatá L. Lipid Dynamics in Pancreatic β-Cells: Linking Physiology to Diabetes Onset. Antioxidants & Redox Signaling [Internet]. 2024 [cited 2024 Dec 3];41:865–89. Available from: https://www.liebertpub.com/doi/https://doi.org/10.1089/ars.2024.0724
163. Pantopoulos K. Inherited disorders of iron overload. Frontiers in nutrition [Internet]. 2018 [cited 2024 Dec 3];5:103. Available from: https://www.frontiersin.org/articles/https://doi.org/10.3389/fnut.2018.00103/full
164. Balakrishnan S, Dhavamani S, Prahalathan C. β-Cell specific transcription factors in the context of diabetes mellitus and β-cell regeneration. Mechanisms of development [Internet]. 2020 [cited

2024 Dec 3];163:103634. Available from: https://www.sciencedirect.com/science/article/pii/S0925477320300393
165. Taneera J, Ali A, Hamad M. The Role of Estrogen Signaling in Cellular Iron Metabolism in Pancreatic β Cells. Pancreas [Internet]. 2022 [cited 2024 Dec 3];51:121–7. Available from: https://journals.lww.com/pancreasjournal/fulltext/2022/02000/the_role_of_estrogen_signaling_in_cellular_iron.4.aspx
166. Gáll T, Balla G, Balla J. Heme, heme oxygenase, and endoplasmic reticulum stress—a new insight into the pathophysiology of vascular diseases. International journal of molecular sciences [Internet]. 2019 [cited 2024 Dec 3];20:3675. Available from: https://www.mdpi.com/1422-0067/20/15/3675
167. Schipper HM, Song W. A heme oxygenase-1 transducer model of degenerative and developmental brain disorders. International journal of molecular sciences [Internet]. 2015 [cited 2024 Dec 3];16:5400–19. Available from: https://www.mdpi.com/1422-0067/16/3/5400
168. An J-R, Wang Q-F, Sun G-Y, Su J-N, Liu J-T, Zhang C et al. The Role of Iron Overload in Diabetic Cognitive Impairment: A Review. DMSO [Internet]. 2023 [cited 2024 Dec 3];Volume 16:3235–47. Available from: https://www.dovepress.com/the-role-of-iron-overload-in-diabetic-cognitive-impairment-a-review-peer-reviewed-fulltext-article-DMSO
169. Marku A, Galli A, Marciani P, Dule N, Perego C, Castagna M. Iron metabolism in pancreatic beta-cell function and dysfunction. Cells [Internet]. 2021 [cited 2024 Dec 3];10:2841. Available from: https://www.mdpi.com/2073-4409/10/11/2841
170. Ježek P, Jabůrek M, Plecitá-Hlavatá L Contribution of Oxidative Stress and Impaired Biogenesis of Pancreatic β-Cells to Type 2 Diabetes., Antioxidants. & Redox Signaling [Internet]. 2019 [cited 2024 Dec 3];31:722–51. Available from: https://www.liebertpub.com/doi/https://doi.org/10.1089/ars.2018.7656
171. Day EA, Ford RJ, Steinberg GR. AMPK as a therapeutic target for treating metabolic diseases. Trends in Endocrinology & Metabolism [Internet]. 2017 [cited 2025 Feb 4];28:545–60. Available from: https://www.cell.com/trends/endocrinology-metabolism/fulltext/S1043-2760(17)30068-1
172. Hardie DG. AMP-activated protein kinase: a master switch in glucose and lipid metabolism. Rev Endocr Metab Disord. 2004;5(2):119–25. https://doi.org/10.1023/B:REMD.0000021433.63915.bb.
173. Wu L, Zhang L, Li B, Jiang H, Duan Y, Xie Z et al. AMP-activated protein kinase (AMPK) regulates energy metabolism through modulating thermogenesis in adipose tissue. Frontiers in physiology [Internet]. 2018 [cited 2024 Dec 3];9:122. Available from: https://www.frontiersin.org/articles/https://doi.org/10.3389/fphys.2018.00122/full
174. Huang J, Simcox J, Mitchell TC, Jones D, Cox J, Luo B et al. Iron regulates glucose homeostasis in liver and muscle via AMP-activated protein kinase in mice. The FASEB Journal [Internet]. 2013 [cited 2024 Dec 3];27:2845. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3688748/
175. Chen Z, Cao B, Liu L, Tang X, Xu H. Association between obesity and anemia in an nationally representative sample of United States adults: a cross-sectional study. Frontiers in Nutrition [Internet]. 2024 [cited 2024 Dec 3];11:1304127. Available from: https://www.frontiersin.org/articles/https://doi.org/10.3389/fnut.2024.1304127/full
176. Rajabnia M, Hajimirzaei SM, Hatamnejad MR, Shahrokh S, Ghavami SB, Farmani M, et al. Obesity, a challenge in the management of inflammatory bowel diseases. Immunol Res. 2022;70:742–51. https://doi.org/10.1007/s12026-022-09315-7.
177. Reichert CO, da Cunha J, Levy D, Maselli LMF, Bydlowski SP, Spada C. Hepcidin: homeostasis and diseases related to iron metabolism. Acta Haematol. 2017;137:220–36.
178. Yao J, Wu D, Qiu Y. Adipose tissue macrophage in obesity-associated metabolic diseases. Frontiers in immunology [Internet]. 2022 [cited 2024 Dec 3];13:977485. Available from: https://www.frontiersin.org/articles/https://doi.org/10.3389/fimmu.2022.977485/full
179. Gotardo ÉMF, dos SANTOS AN, Miyashiro RA, Gambero S, Rocha T, Ribeiro ML et al. Mice that are fed a high-fat diet display increased hepcidin expression in adipose tissue. Journal of nutritional science and vitaminology [Internet]. 2013 [cited 2024 Dec 3];59:454–61. Available from: https://www.jstage.jst.go.jp/article/jnsv/59/5/59_454/_article/-char/ja/
180. Sagar P, Angmo S, Sandhir R, Rishi V, Yadav H, Singhal NK. Effect of hepcidin antagonists on anemia during inflammatory disorders. Pharmacol Ther. 2021;226:107877.
181. Nili M, David L, Elferich J, Shinde U, Rotwein P. Proteomic analysis and molecular modelling characterize the iron-regulatory protein haemojuvelin/repulsive guidance molecule c. Biochemical Journal [Internet]. 2013 [cited 2024 Dec 3];452:87–95. Available from: https://portlandpress.com/biochemj/article-abstract/452/1/87/46184
182. Rochette L, Gudjoncik A, Guenancia C, Zeller M, Cottin Y, Vergely C. The iron-regulatory hormone hepcidin: a possible therapeutic target? Pharmacol Ther. 2015;146:35–52.
183. Moreno-Navarrete JM, Moreno M, Puig J, Blasco G, Ortega F, Xifra G et al. Hepatic iron content is independently associated with serum hepcidin levels in subjects with obesity. Clinical Nutrition [Internet]. 2017 [cited 2024 Dec 3];36:1434–9. Available from: https://www.sciencedirect.com/science/article/pii/S0261561416312626?casa_token=BsytCWP-XREAAAAA:11esd6-1hNxxs_sDda6npbZFzk98BFmg0QKiKlg1Myk7FfSGFSueH5HNP0iL-Dv-k-QHXbF6QA
184. Xiao L, Luo G, Li H, Yao P, Tang Y. Dietary iron overload mitigates atherosclerosis in high-fat diet-fed Apolipoprotein E knockout mice: role of dysregulated hepatic fatty acid metabolism. Biochimica et biophysica acta (BBA)-Molecular and cell biology of lipids. 2021;1866:159004.
185. Iannone F, Lapadula G. Obesity and inflammation-targets for OA therapy. Current drug targets [Internet]. 2010 [cited 2024 Dec 3];11:586–98. Available from: https://www.ingentaconnect.com/content/ben/cdt/2010/00000011/00000005/art00008
186. Martínez-Uña M, López-Mancheño Y, Diéguez C, Fernández-Rojo MA, Novelle MG. Unraveling the role of leptin in liver function and its relationship with liver diseases. International journal of molecular sciences [Internet]. 2020 [cited 2024 Dec 3];21:9368. Available from: https://www.mdpi.com/1422-0067/21/24/9368
187. Chung B, Matak P, McKie AT, Sharp P. Leptin increases the expression of the iron regulatory hormone hepcidin in HuH7 human hepatoma cells. The Journal of nutrition [Internet]. 2007 [cited 2024 Dec 3];137:2366–70. Available from: https://www.sciencedirect.com/science/article/pii/S0022316622094147
188. Lin D, Medeiros DM. The microbiome as a major function of the gastrointestinal tract and its implication in micronutrient metabolism and chronic diseases. Nutr Res. 2023;112:30–45.
189. Schoeler M, Caesar R. Dietary lipids, gut microbiota and lipid metabolism. Rev Endocr Metab Disord. 2019;20:461–72.
190. Flint HJ, Duncan SH, Scott KP, Louis P. Links between diet, gut microbiota composition and gut metabolism. Proc Nutr Soc. 2015;74:13–22.
191. Li S, You J, Wang Z, Liu Y, Wang B, Du M, et al. Curcumin alleviates high-fat diet-induced hepatic steatosis and obesity in association with modulation of gut microbiota in mice. Food Res Int. 2021;143:110270.
192. Liang H, Jiang F, Cheng R, Luo Y, Wang J, Luo Z, et al. A high-fat diet and high-fat and high-cholesterol diet may affect glucose and

lipid metabolism differentially through gut microbiota in mice. Exp Anim. 2021;70:73–83.
193. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. J Res Med Sciences: Official J Isfahan Univ Med Sci. 2014;19:164.
194. Yilmaz B, Li H. Gut microbiota and iron: the crucial actors in health and disease. Pharmaceuticals. 2018;11:98.
195. Malesza IJ, Bartkowiak-Wieczorek J, Winkler-Galicki J, Nowicka A, Dzięciołowska D, Błaszczyk M, et al. The dark side of iron: the relationship between iron, inflammation and gut microbiota in selected diseases associated with iron deficiency anaemia—a narrative review. Nutrients. 2022;14:3478.
196. Jaeggi T, Kortman GA, Moretti D, Chassard C, Holding P, Dostal A, et al. Iron fortification adversely affects the gut microbiome, increases pathogen abundance and induces intestinal inflammation in Kenyan infants. Gut. 2015;64:731–42.
197. Seyoum Y, Baye K, Humblot C. Iron homeostasis in host and gut bacteria – a complex interrelationship. Gut Microbes. 2021;13:1874855.
198. Xiong Q, Zhao J, Tian C, Ma W, Miao L, Liang L, et al. Regulation of a high-iron diet on lipid metabolism and gut microbiota in mice. Animals. 2022;12:2063.
199. Gu K, Wu A, Yu B, Zhang T, Lai X, Chen J, et al. Iron overload induces colitis by modulating ferroptosis and interfering gut microbiota in mice. Sci Total Environ. 2023;905:167043.
200. Rodríguez C, Romero E, Garrido-Sanchez L, Alcaín-Martínez G, Andrade R, Taminiau B, et al. Microbiota insights in *Clostridium difficile* infection and inflammatory bowel disease. Gut Microbes. 2020;12:1725220.
201. Rodrigues VF, Elias-Oliveira J, Pereira ÍS, Pereira JA, Barbosa SC, Machado MSG, et al. *Akkermansia muciniphila* and gut immune system: a good friendship that attenuates inflammatory bowel disease, obesity, and diabetes. Front Immunol. 2022;13:934695.
202. Abenavoli L, Scarpellini E, Colica C, Boccuto L, Salehi B, Sharifi-Rad J, et al. Gut microbiota and obesity: a role for probiotics. Nutrients. 2019;11:2690.
203. You H, Tan Y, Yu D, Qiu S, Bai Y, He J, et al. The therapeutic effect of SCFA-mediated regulation of the intestinal environment on obesity. Front Nutr. 2022;9:886902.
204. Jia X, Xu W, Zhang L, Li X, Wang R, Wu S. Impact of Gut Microbiota and Microbiota-Related Metabolites on Hyperlipidemia. Front Cell Infect Microbiol [Internet]. 2021 [cited 2025 Jul 19];11. Available from: https://www.frontiersin.org/journals/cellular-and-infection-microbiology/articles/https://doi.org/10.3389/fcimb.2021.634780/full
205. Peng L, Li Z-R, Green RS, Holzman IR, Lin J. Butyrate Enhances the Intestinal Barrier by Facilitating Tight Junction Assembly via Activation of AMP-Activated Protein Kinase in Caco-2 Cell Monolayers. J Nutr [Internet]. 2009 [cited 2025 Jul 19];139:1619–25. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2728689/
206. Fujisaka S, Watanabe Y, Tobe K. The gut microbiome: a core regulator of metabolism. J Endocrinol. 2023;256:e220111.
207. Yu Y, Raka F, Adeli K. The role of the gut microbiota in lipid and lipoprotein metabolism. J Clin Med. 2019;8:2227.
208. Long Q, Luo F, Li B, Li Z, Guo Z, Chen Z, et al. Gut microbiota and metabolic biomarkers in metabolic dysfunction-associated steatotic liver disease. Hepatol Commun. 2024;8:e0310.
209. Jian Z, Zeng L, Xu T, Sun S, Yan S, Zhao S, et al. The intestinal microbiome associated with lipid metabolism and obesity in humans and animals. J Appl Microbiol. 2022;133:2915–30.
210. Rivera-Iñiguez I, Panduro A, Roman S, González-Aldaco K. What do we know about nutrient-based strategies targeting molecular mechanisms associated with obesity-related fatty liver disease? Ann Hepatol. 2023;28:100874.
211. Cunningham AL, Stephens JW, Harris DA. A review on gut microbiota: a central factor in the pathophysiology of obesity. Lipids Health Dis. 2021;20:65.
212. Lei L, Zhao N, Zhang L, Chen J, Liu X, Piao S. Gut microbiota is a potential goalkeeper of dyslipidemia. Front Endocrinol (Lausanne). 2022;13:950826.
213. Wang X, Wu Q, Zhong M, Chen Y, Wang Y, Li X, et al. Adipocyte-derived ferroptotic signaling mitigates obesity. Cell Metab. 2025;37:673–e6917.
214. Qi J, Kim J-W, Zhou Z, Lim C-W, Kim B. Ferroptosis affects the progression of nonalcoholic steatohepatitis via the modulation of lipid peroxidation-mediated cell death in mice. Am J Pathol. 2020;190:68–81.
215. Speakman JR. Ferroptosis in adipose tissue: a promising pathway for treating obesity? Cell Metab. 2025;37:560–1.
216. Ma W, Jia L, Xiong Q, Du H. Iron Overload Protects from Obesity by Ferroptosis. Foods [Internet]. 2021 [cited 2025 Jul 19];10:1787. Available from: https://www.mdpi.com/2304-8158/10/8/1787
217. Zhou D, Lu P, Mo X, Yang B, Chen T, Yao Y, et al. Ferroptosis and metabolic syndrome and complications: association, mechanism, and translational applications. Front Endocrinol (Lausanne). 2023;14:1248934.
218. Luo Y, Chen H, Liu H, Jia W, Yan J, Ding W, et al. Protective effects of ferroptosis Inhibition on high fat diet-induced liver and renal injury in mice. Int J Clin Exp Pathol. 2020;13:2041–9.
219. Park GC, Bang S-Y, Kim JM, Shin S-C, Cheon Y-I, Kim KM, et al. Inhibiting ferroptosis prevents the progression of steatotic liver disease in obese mice. Antioxidants. 2024;13:1336.
220. Liu W, Zou H, You D, Zhang H, Xu L. Sodium houttuybonate promotes the browning of white adipose tissue by inhibiting ferroptosis via the AMPK-NRF2-HO1 pathway. Antioxidants. 2024;13:1057.