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REVIEW ARTICLE

Relationship between Hepcidin and Iron in Diabetes Mellitus and Liver Disorders:Review artical

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ABSTRACT:

Hepcidin, ferritin, and transferrin are among the several proteins that are mostly found in the liver and are involved in the control of iron metabolism. These proteins play a part in iron metabolism and are acute-phase reactants whose expression can change in response to inflammation or hepatic or systemic damage. Pro-inflammatory mediators generated by macrophages, which contribute to the development of peripheral insulin resistance, may have an impact on hepcidin synthesis. Ferroportin-1, the sole known Fe exporter, is bound by circulating hepcidin, which then drives enterocytes and splenic macrophages to internalize and degrade it.

An upward body of data indicates that iron deficiency plays a major role in the emergence of a number of several disorders. Hepcidin and systemic iron homeostasis play a significant role in liver disorders and type-2 diabetes. These include erythropoiesis, infection, inflammation, body iron storage, and plasma iron content. The mechanism and regulation of hepcidin-induced iron overload, as well as associated liver and diabetic disorders, are summed up in this review. Additionally, we outline examples of associations between hepcidin and blood iron levels in a range of metabolic diseases, primarily liver and diabetes.

INTRODUCTION

Because iron (Fe) contributes to a variety of metabolic activities, including energy metabolism, nucleotide synthesis, oxygen transport, and electron transport between cells, it is a necessary trace element for living things and influences genome synthesis [1]. The liver is essential for storing iron. Excess iron can build up in liver cells when there is a pathological increase in the intestinal or hepatocytes' uptake of iron [2]. Fe is essential, but too much of it can be harmful, thus the concentration must be kept within a certain limit. Adults typically have an iron level of about 60 g/dL. For basic physiological systems to operate at their best, Fe metabolic equilibrium is necessary [3]. Ferroptosis is one of the pathological alterations brought on by abnormal Fe metabolism, which primarily manifests as Fe overload or shortage. Ferroptosis is a non-apoptotic cell death process that depends on iron, and is typified by the buildup of lipid hydroperoxides and iron overload [4].

Ferroptosis is implicated in the onset, progression, and consequences of type 2 diabetic mellitus (T2DM), according to a number of studies [3]. Hyperglycemia and insulin resistance are the hallmarks of type 2 diabetes, a metabolic condition that is growing more prevalent [1]. The development of type 2 diabetes (T2D) and aberrant glucose metabolism can both be attributed to systemic Fe overload. Few studies have thoroughly examined the relationships between serum hepcidin concentrations and Fe metabolism

indicators and the risk of developing type 2 diabetes, despite the fact that hepcidin is the master regulator of systemic Fe homeostasis [5].

The operation of several organs is negatively impacted by Fe overload, which causes severe oxidative stress. Fe deposition, specifically, can affect the function of pancreatic β-cells, which can lead to a reduction in insulin production, the development of DM hepcidin concentrations with Fe metabolism characteristics, and an increased risk of developing type-2 diabetes. Growing epidemiological data indicates that a higher incidence of T2D is caused by Fe overload [6].

The buildup of iron in liver tissue is a common feature of many liver illnesses, such as metabolic linked fatty liver disease, alcohol-associated liver disease, and infection-induced liver fibrosis [7]. The potential involvement of iron in liver fibrosis has been the subject of an increasing number of investigations. For instance, research has shown that Fe overload directly causes collagen deposition and activation, which advances cirrhosis in mice. Additionally, hepatocytes and macrophages loaded with Fe release a variety of factors that accelerate liver fibrosis by promoting the activation of HSCs and the deposition of extracellular matrix [8]. The most frequent cause of chronic liver disease in individuals with type 2 diabetes is metabolic dysfunction-associated steatotic liver disease, which is strongly linked to poor cardiovascular outcomes and elevated levels of iron storage biomarkers in the blood stream (particularly when metabolic dysfunction-associated steato-hepatitis is present along with rising liver fibrosis levels) [9, 10].

The primary modulator of systemic iron levels is hepcidin. It can be produced via extrahepatic or hepatic routes [11]. In the liver, it is primarily produced as an 84-amino acid prepropeptide, which is subsequently converted into a 60- to 64-residue prohepcidin peptide and, ultimately, into the mature and physiologically useful 25-amino acid hepcidin. Hepatocytes are the primary source of hepcidin, which is elevated in iron excess, infections, inflammation, chronic kidney illness, metabolic problems associated with obesity, and chronic liver diseases. Proinflammatory mediators generated by macrophages can influence hepcidin synthesis and contribute to the development of peripheral insulin resistance [12]. Ferroportin-1, the sole known iron exporter, is bound by circulating hepcidin, which leads it to be internalized and degraded by splenic macrophages and enterocytes [13]. When hepcidin is lost, ferroportin-1 is not down-regulated, which causes excessive iron absorption and hereditary hemochromatosis [14]. Men with T2D or reduced glucose tolerance have noticeably greater serum prohepcidin levels [15]. Prohepcidin levels in various populations have been measured in the past, but no meaningful correlations between prohepcidin levels and Fe status or absorption have been discovered. This implies that prohepcidin is not a good indicator of Fe status and absorption [16]. According to a more recent study, the mature form of serum hepcidin, as opposed to prohepcidin, is a more sensitive and trustworthy indicator for figuring out Fe absorption and concentrations [17]. The induction of type 2 diabetes is linked to a notable rise in hepcidin levels [12].

Although hepcidin's regulatory action on hepatocytes is still mostly unclear, previous research has shown that it contributes to the development of liver fibrosis via controlling HSC activity [18]. Because it controls iron metabolism and may be a target for treatment, hepcidin has been demonstrated to be a significant biochemical marker in the diagnosis of liver fibrosis [19]. Hepcidin functions as an endogenous antifibrotic hepatokine by blocking Smad3 phosphorylation in HSCs via AKT [20]. Even though the main event in fibrosis is the activation of HSCs, surrounding cells like hepatocytes have an impact on the biological status of HSCs, and their damage and regeneration are crucial to the development of fibrosis. As CCl4-induced liver fibrosis and bile

duct ligation progressed, serum hepcidin levels rose noticeably [18].

Serum ferritin levels are frequently employed as a clinical biomarker to assess body Fe status. Serum ferritin concentrations are elevated in T2D patients, according to several studies, and relatively high ferritin levels are linked to an increased risk of T2D in healthy people. However, because previous research used assays that are not selective for biologically functional hepcidin, it is still unclear how hepcidin concentrations fluctuate in T2D patients and whether hepcidin is linked to risks of T2D. Furthermore, hepcidin expression may be influenced by a number of regulatory pathways that regulate it as well as systemic inflammation that occurs concurrently with type 2 diabetes [5, 9].

Finally, although though hepcidin and iron are linked to a number of liver diseases and problems associated with diabetes, we concentrate on their roles in the pathogenesis of these conditions.

Overview of iron metabolism

Hemoglobin, myoglobin, cytochromes, nitric oxide synthase, and several other enzymes necessary for the production of ATP in all cells are made of iron. Every second, two to three million red blood cells are created, and each one needs 30–40 mg of iron to be supplied to the erythron in order to produce 30 pg of hemoglobin, or 6 g of hemoglobin every day. Therefore, hemoglobin contains 2–2.5g of the 3–4g of Fe overall in the human body, hepatocytes and macrophages have 0.5–1g, and other cell types contain 0.5g of total myoglobin, ferritin, and iron-containing enzymes [5, 18].

In order to benefit from iron for metabolic and other redox processes, early organisms evolved. For many metabolic processes, iron is an essential cofactor. One of the most crucial indicators of good health is an iron profile. Numerous diseases are at risk due to altered iron profiles. Many cellular structures are harmed by excessive iron buildup in the body, which also results in oxidative damage and other issues [21]. Plasma transferrin (Tf) is the source of iron for the majority of mammalian cells. The transferrin receptor 1 (TfR1) binds to iron to produce a trivalent iron complex (Tf-Fe3+), which is then delivered to a tissue cell that includes a TfR. Tf also serves as the primary carrier of iron to cells and restricts the generation of free radicals. Transferrin that contains iron attaches itself to TfR1 on the cell surface and uses endocytosis to move its contents into the cytoplasm. [2].

The 76-kDa glycoprotein known as human Tf is mostly produced in the liver and has a half-life of around eight days in serum [2, 21]. Fe intake, intracellular use, and storage must be balanced to maintain Fe homeostasis. Duodenal enterocytes absorb dietary iron, which then binds to plasma. Tf saturation is maintained at physiological levels via the Fe homeostasis system. Less than 10% of the Fe demand during Fe metabolism is satisfied by intestinal absorption; ferroportin exports the remaining Fe [3, 22]. Hepcidin, a peptide hormone frequently released by hepatocytes, controls ferroportin [13, 22]. However, in pathological settings, the intestinal or hepatocytes' intake of iron rises. Hepatocytes store excess iron, which causes ROS generation, which is how it causes toxicity [23].

Numerous harmful OH are created in the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+}$ + hydroxyl radicals [OH] + OH^-) [24]. In order to destroy cells, OH causes lysosome, cytoplasmic, nuclear, and mitochondrial membrane damage. It also activates caspases, which leads to cell death, and excessive oxidation of aliphatic chains [25].Iron is a powerful oxidant that is required for metabolism, and intricate systems to control its absorption, storage, and bioavailability have also developed [26] (Fig. 1).

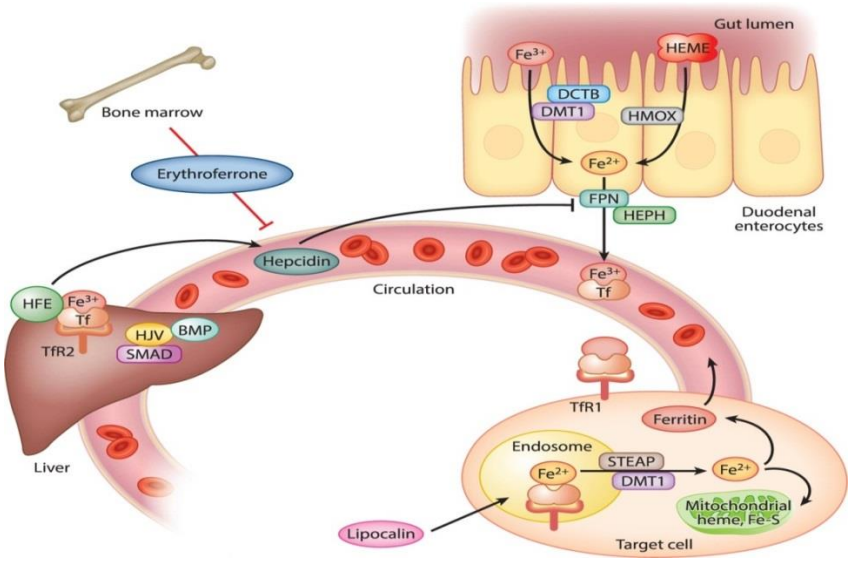

Fig. 1. Iron homeostasis. Duodenal cytochrome B (DCTB) converts intestinal free ferric (Fe3+) iron to Fe2+, which is then taken up by the cell via the divalent metal transporter 1 (DMT1). Hemeoxygenase (HMOX) releases iron, and dietary heme is directly absorbed. Through the export channel ferroportin (FPN), iron leaves the enterocyte. Iron binds to transferrin (Tf) in the bloodstream after being oxidized by hephaestin (HEPH), and Tf then binds to target cell transferrin receptors (TfR) 1 and 2. Following acidification in the endosome, iron is liberated from TfRl, reduced by six-transmembrane epithelial antigen of the prostate (STEAP), and then transported into the cytosol via DMT1 for usage (e.g., for heme or Fe-S-cluster production). Ferritin sequesters excess iron. Tissue iron reserves are indicated by apo-ferritin, which is released into the bloodstream. In the fifth, Tf binds TfR2 and the protein HFE and uses the SMAD signal transduction pathway, hemojuvelin (HJV), and bone morphogenic protein (BMP) to signal the synthesis of hepcidin. Hepcidin functions as a negative feedback regulator of more intestinal iron absorption by inducing down-regulation of FPN. The figure was modified with consent [27].

Hepcidin and iron

For many years, it has been understood that there is a physiological mechanism that preserves iron homeostasis by increasing dietary iron absorption when iron stores are low and decreasing absorption when iron stores are full. When hepcidin (gene name Hamp) was discovered in 2001, it became clear who the main regulator of these events. Understanding of iron diseases has been completely transformed by the 2001 discovery of the iron-regulatory hormone hepcidin, and measuring it should help with diagnosis and therapy of these problems [11].

Hepatocytes release hepcidin, which attaches to membrane ferroportin (FPN) and causes internalization, ubiquitination, and degradation of FPN, hence influencing serum iron levels and cell iron release [2]. Two important modulators of iron metabolism are hepcidin and FPN. However, a number of earlier investigations have demonstrated that iron metabolism disorders may play a role in the development of type 2 diabetes. Cell types involved in iron metabolism, such as placental syncytiotrophoblasts, liver and spleen macrophages, and the basolateral membrane of duodenal enterocytes, have high expression of FPN. Hepcidin and other chemicals that impact FPN are released by the body in response to iron overload in order to decrease iron outflow. Otherwise, by blocking intestinal iron absorption and macrophage iron circulation,

hepcidin, a key hormone that regulates iron, regulates plasma iron levels [28].

The first way that liver cells react to iron is indirectly through hepatic sinusoidal endothelial cells, which produce iron-regulated bone morphogenetic protein (BMP) [29]. Hepcidin expression is dependent on the BMP pathway. Hepcidin expression appears to be modulated by BMPs via two distinct mechanisms. The first one explains how hepatocytes can respond to elevated serum iron by producing more Hamp mRNA. Holo-Tf is created when serum iron circulates attached to transferrin (Tf). On the plasma membrane of hepatocytes, HFE, the byproduct of the gene whose mutations cause the most prevalent type of hereditary hemochromatosis (HH), combines with transferrin receptor 1 (TFR1). It has been proposed that holo-Tf's interaction with TFR1 causes HFE to separate from its complex with TFR1, enabling HFE to attach to transferrin receptor 2 (TFR2), which is then followed by the HFE-TFR2 complex attaching to membrane-bound hemojuvelin, the BMP coreceptor [30].

A different investigation shown that the expression of TfR1, transferrin receptor 2 (TfR2), and HFE proteins on the cell surface allows hepatocytes to directly sense iron. As serum iron levels rise, TfR2 expression surpasses that of TfR1, and Tf-Fe (III) concurrently combines with both TfR1 and TfR2 to boost TfR2 stability. Furthermore, the principal mechanism by which HFE controls iron metabolism is through influencing hepcidin expression, which in turn controls iron absorption [30].

BMP2 is thought to be involved in later stages of this signaling pathway that modify the expression of the hepcidin gene. According to additional research, the BMP subfamily uses receptor-activated Smads to signal and control the expression of hepcidin. The liver's sinusoidal endothelial cells are the source of BMP6, and the iron burden increases BMP6 synthesis. After binding to BMP II receptors, BMP6 phosphorylates BMP I receptors, initiates the Smad1/5/8 pathway, forms isomer complexes with Smad4, moves into the nucleus, and triggers hepcidin transcription [20, 31]. Previous research has indicated that hepcidin expression levels in the liver and adipose tissue are unaffected by diabetes [32]. Others found that individuals with diabetes who also had higher serum ferritin and IL-6 levels had significantly greater serum hepcidin levels [33]. Furthermore, there is currently no information on the association between circulating hepcidin concentrations and the risk of cardiovascular events and overall mortality in individuals with type 2 diabetes mellitus (T2DM), a patient population at high risk of major adverse cardiovascular events, in whom cardiovascular risk is frequently unpredictable [10]. Hepcidin overproduction causes ferroportin to be down-regulated, which results in intracellular iron sequestration and a reduction in iron intake. Excess iron may worsen IR and cause oxidative stress in hepatocytes [34].

Hepcidin production rises in response to inflammation or illness. Interleukin-6 (IL-6) often mediates the induction of hepcidin during inflammation. Hepcidin during inflammation must be induced by IL-6, and the cytokine itself has the ability to quickly cause iron deficient anemia. It has been established that there is some interaction between the BMP/SMAD signaling pathway and the IL-6-induced signal transducer and activator of the transcription 3 (STAT-3) signaling pathway [35]. STAT-3 and C/EBPα binding sites are found on the HAMP promoter, and the two pathways converge throughout the inflammatory process (Fig. 2).

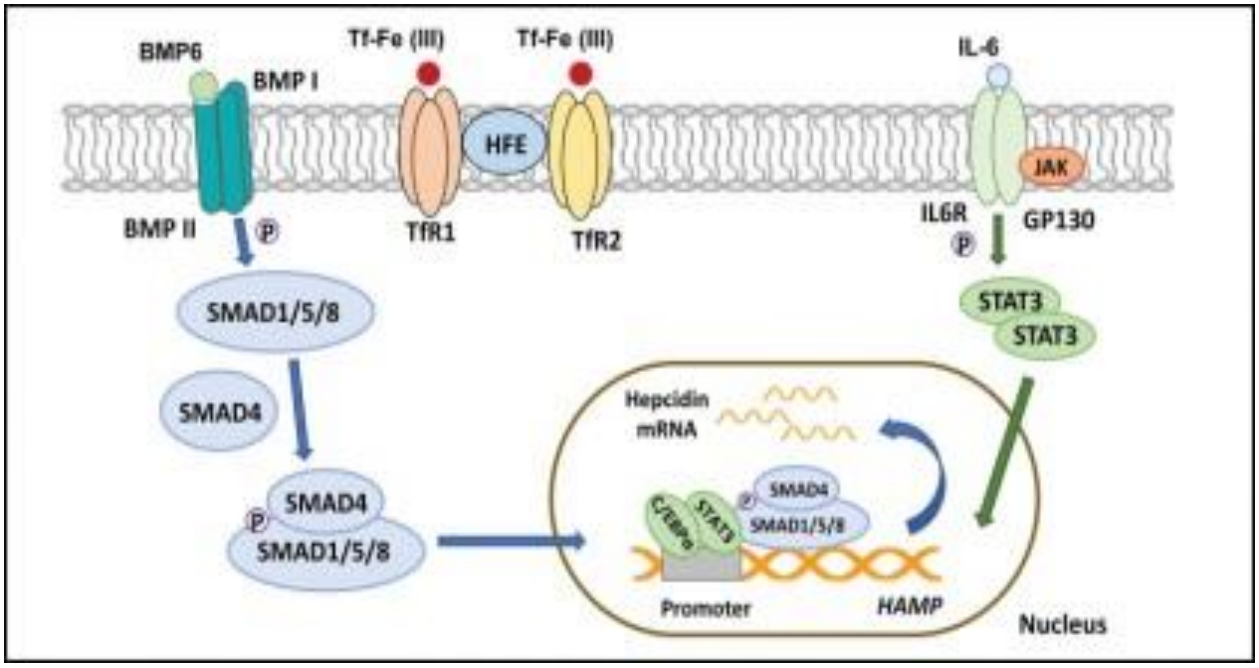

Fig. 2: Multiple pathways regulate hepcidin expression [36].

According to other researchers, the bone morphogenetic protein (BMP) family is essential for integrating signals that control the expression of hepcidin in response to iron levels. By binding to BMP type II receptors, certain BMPs phosphorylate BMP type I receptors, triggering the SMAD 1/5/8 pathway and forming a heteromeric complex with Smad4 that translocates to the nucleus to promote the expression of the hepcidin gene [37, 38].

Hepcidin expression temporarily rises in response to acute liver damage (Fig. 3).

Elevations of inflammatory mediators, including IL-6, preceded increases in Hamp mRNA levels in certain models, indicating that hepcidin's action as an acute-phase reactant is typical of induction under these conditions [39]. According to this perspective, hypoferremia is a feature of the majority of the models covered here. But the fact that hypoferremia was frequently seen to occur before increases in Hamp mRNA and/or without detectable increases in circulating hepcidin levels, as previously mentioned, indicates that other factors may be at play in controlling iron levels in these acute-phase models [38].

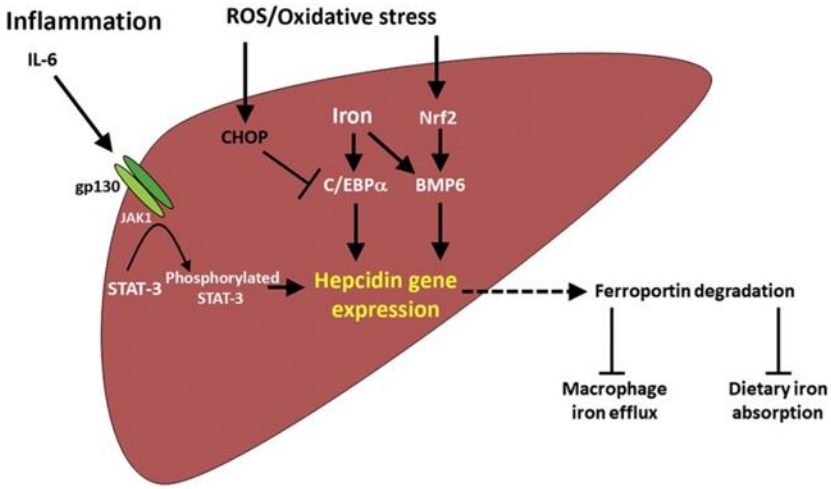

Fig. 3. Factors that control the expression of hepatic hepcidin in response to liver damage. Hepcidin expression is increased in a number of acute liver injury types through STAT3 activation triggered by inflammatory cytokines, specifically IL-6. https://ars.els-cdn.com/content/image/1-s2.0-S0002944021001565-gr1_lrg.jpg

Iron overload was caused on by larger red blood cells and increased cellular hemoglobin levels. Despite enhanced iron storage, this illness with concurrent iron overload and elevated erythropoiesis exhibits lower hepcidin expression than anticipated. In these disorders, hepcidin expression is linked to iron overload and indicates the presence of "red-like factors" that control iron metabolism [40]. Hepcidin expression in the body is regulated by erythropoietin (EPO) in two ways: 1. EPO decreases transferrin's iron saturation and promotes iron incorporation into the bone marrow's erythrocyte precursors, which suppresses hepcidin production by lowering iron burden. 2. By encouraging bone marrow erythroblasts to create ERFE, which partially inhibits the liver's BMP-SMAD pathway, EPO also contributes to the reduction of hepcidin. Furthermore, hepcidin transcription can be directly inhibited by hypoxia-inducible factors, which interfere with BMP signal transduction and reduces hepcidin activity (Fig.4).

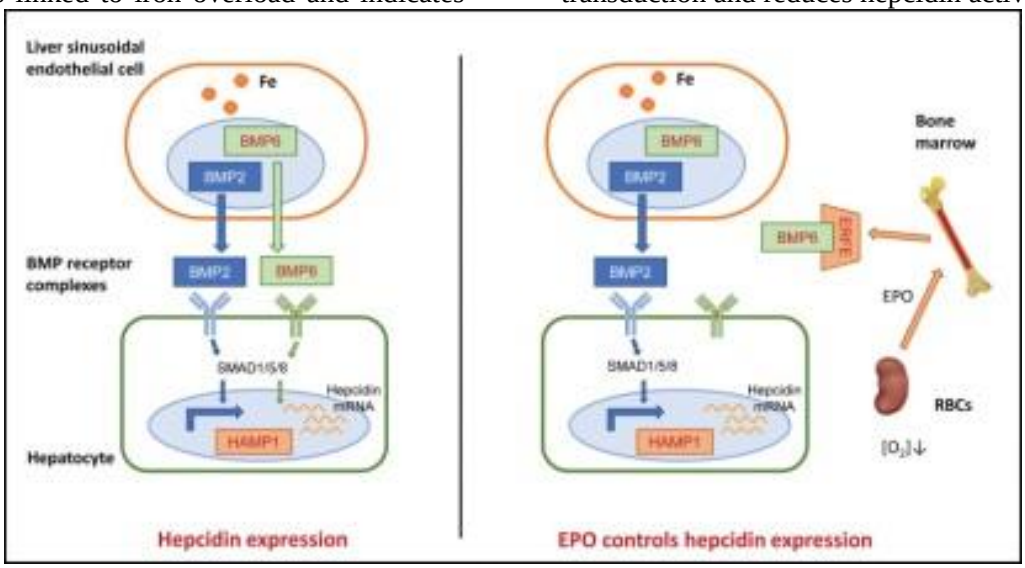

Fig. 4: Hepcidin expression is modulated by BMP/SMAD signaling: BMP receptors on hepatocyte cell membranes phosphorylate cytosolic SMADs (SMAD1, SMAD5, and SMAD8) that enter the nucleus complexed with SMAD4 and trigger the transcriptional response, which includes hepcidin (HAMP).ERFE prevents the induction of hepcidin expression caused by BMP5, BMP6, and BMP7. BMP = bone morphogenetic protein, ERFE = erythroferrone [36].

Iron metabolism and type 2 diabetes

Unquestionably, macronutrients contribute to an elevated risk of type 2 diabetes mellitus (T2DM); however, iron, a micronutrient, is also a risk factor, both in its wide range of normal levels and in pathological excess or deficiency. All prevalent types of diabetes are characterized by a loss of insulin secretion, which is also linked to iron-related diabetes brought on by either dietary excess or pathologic iron overload. This reduction of insulin secretion is caused by a number of processes, as is particularly true for type-2 diabetes [41, 42].

Hepcidin, transferrin, ferritin, transferrin receptor, and other markers of iron metabolism can all have a direct or indirect impact on the onset and progression of type 2 diabetes. Nevertheless, the findings that described the relationship between iron metabolism and type 2 diabetes varied by sex and ethnicity [43]. Serum ferritin levels were substantially lower in Asian males with diabetes than in those without, but significantly higher in women with diabetes than in women without diabetes across all racial/ethnic groups [44].

The amount of iron in islet β-cells is directly correlated with blood sugar levels. However, the islet β-cells are more prone to deposit iron due to their increased expression levels of iron transport proteins when compared to other tissue cells [6]. Excessive iron may damage insulin production and raise the likelihood of insulin resistance (IR) by causing excessive oxidative stress and encouraging islet β-cell death. One established risk factor for type-2 diabetes is iron overload [45]. Patients with hereditary hemochromatosis (HH) may be the first to be described with IR. Iron accumulation in pancreatic β cells is the mechanism of HH, and HH causes cell death, which results in diabetes [22]. According to a comprehensive study, plasma Tf may have a direct or indirect relationship with the development of diabetes, and the TfR to ferritin ratio was adversely correlated with the risk of T2DM [14]. Higher plasma serum ferritin levels were substantially linked to an elevated risk of type 2 diabetes, according to cohort research. These findings lend credence to iron consumption and storage as a marker of type 2 diabetes, which may enable early clinical identification [46]. Maintaining adequate iron metabolism is essential for blood glucose stability because of the connection between iron metabolism and glucose homeostasis [3].

Because altered glucose metabolism changed the iron profile and vice versa, there is a close link between the two conditions. The changed iron profile or the fact that free iron causes oxidative stress and inflammatory cytokines is the origin of this reciprocal interaction [47].

Numerous microvascular (such as neuropathy, nephropathy, and retinopathy), macrovascular (such as atherosclerosis), and other consequences (such as diabetic cardiomyopathy) conditions affect people with diabetes [48]. Free radicals, such as free iron, cause oxidative damage, which in turn causes the different difficulties caused by reactive oxygen species. One of the most crucial micronutrients for overall health is iron, and problems with iron metabolism can cause lipid-protein oxidation and damage to the red blood cell membrane [49]. Numerous studies concluded that diabetes was caused by reactive free iron or iron overloads [50]. It is yet unclear how precisely the changed iron metabolism causes conditions like diabetes. However, discovered a negative correlation between serum ferritin concentration and insulin sensitivity, indicating a direct relationship between insulin resistance and total body iron reserves [51]. Iron metabolism is one of the numerous metabolic functions that are adversely affected by hyperglycemia in individuals with type 2 diabetes [46].Iron overload in T2DM has been documented in a number of investigations [37].

Free iron radicals cause biomolecules to oxidize, producing hydroxyl radicals (OH*) through Haber-Weiss and Fenton processes. These free radicals harm nucleic acids and proteins found in cellular membranes. Insulin resistance and ultimately type 2 diabetes are

caused by these events [52].Proteins are glycated non-enzymatically by the free OH*. Advanced glycation end products (AGEs) are produced when proteins undergo non-enzymatic glycation, which is followed by a sequence of events and rearrangements. These mechanisms cause the generation of ROS, as does the interaction between AGEs and their receptors (RAGE). The pool of free iron is induced by the glycated transferrin's reduced capacity to bind Fe^{3+}. Ferritin production is also aided by oxidative stress and free iron [21].

Iron and liver diseases

Iron excess and hepatic inflammatory activation are linked to alcoholic liver disease (ALD). One significant metabolic mediator during the course of ALD formation is the receptor for advanced glycation end products (RAGE). Iron metabolism pathways were surprisingly changed, with decreased iron export (FPN1/Hepcidin) and increased iron intake (Tf/TfR) and storage (Ferritin) [53]. Iron is predominantly found in hepatocytes and iron deposition is very modest in ALD of early stages, such as fatty liver and fibrosis. These results suggest that alcohol or its metabolites mainly impact and dysregulate the body's iron metabolism, including intestinal iron absorption and hepatocyte iron uptake, in a particular way, such as through the recently identified hormone hepcidin. ROS generation is thought to be the primary cause of the basic pathophysiology of ALD. Superoxide ($O2^{-}$) is created during the oxidation of ethanol and undergoes the Fenton reaction with free iron to become the most powerful oxidant, hydroxyl radical (OH^{-}) [25]. In fact, carbonyl iron supplementation promotes cirrhosis and fibrosis in the intragastric infusion model of ALD [54].

Hepcidin production is also regulated by inflammation, which is consistent with the function of hepcidin-mediated iron redistribution in host defense. In iron-restrictive anemia, such as those linked to inflammation, chronic renal disease, and certain types of cancer, elevated hepcidin levels in plasma are harmful. Ineffective erythropoiesis and iron overload in HH are caused by hepcidin deficiency. Potential targets for the identification and management of iron problems and anemia include hepcidin, ferroportin, and their regulators [55].

The clinical condition known as non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD) is distinguished by histological alterations that are almost exactly the same as those brought on by alcohol consumption. About 25% of Americans are obese, and at least 20% of those who are obese also have hepatic steatosis. It is hypothesized that both obesity and steatosis influence the course of liver disease [56].

Following increased iron absorption from the small intestine, alcohol-loading may down regulate the production of hepcidin by interfering with the detecting signal of inflammatory cytokines. Regarding the mechanism by which alcohol down regulates hepcidin, a decrease in hepcidin expression in the liver of mice is associated with an increase in ferroportin 1 and DMT1, as well as a decrease in the DNA-binding activity of CCAAT/enhancer-binding protein and hepcidin promoter activity [56, 57].

The primary risk factors for hepatocellular carcinoma (HCC) include liver cirrhosis and chronic hepatitis B virus (HBV) infection. Up to 27.1% of patients with CHB have high Tf saturation, and 48.7% have liver iron deposition, making iron overload a prevalent symptom [58]. Regardless of transaminase levels, patients with positive serum HBsAg have greater serum iron levels than those without HBsAg. Iron storage in CHB patients includes high ferritin and serum iron levels as well as ongoing iron buildup in the liver. Iron may potentially have an impact on HBV growth.In well-compensated CHB infections, liver iron deposition and an elevated serum iron index are common, particularly in men and HDV patients [2].

Since cirrhosis is found in 70% of cases of hepatic cell carcinoma (HCC) worldwide, it is a significant risk factor for HCC. Iron deposition

in liver regeneration nodules is linked to HCC in patients with liver cirrhosis who do not have a clear history [59]. Excess liver iron can cause liver cancer or tumor transformation in cirrhotic livers. Particularly in patients who consume large amounts of alcohol, elevated serum transferrin saturation is linked to higher rates of liver cirrhosis and liver cancer [60]. Nonetheless, the majority of individuals with HBV-related HCC still have serum iron levels that fall within the normal range.

CONCLUSION

In cases of pathologic iron overload, iron is a known risk factor for liver problems and diabetes. Adipose tissue, hepatocytes, and pancreatic β cells are among the organs and cells whose glucose homeostasis has been demonstrated to be impacted by iron. Elevated iron levels in the liver control alterations in insulin sensitivity and hepatic glucose synthesis. A prospective addition to the current suite of iron status diagnostic assays is hepcidin. The risk of developing type-2 diabetes was raised by the elevated ferritin and hepcidin levels.

Conflict of interest

All authors have reviewed and approved the paper for publication, and they all state that they have no conflicting any financial or personal relationships with other people or organizations that could inappropriately influence their actions.

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