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Mini Review

RELATIONSHIP BETWEEN IRON METABOLISM, FERROPTHOSIS AND DIABETES MELLITUS

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ABSTRACT
Ferroptosis is a newly discovered form of cell death, which is closely related to the high accumulation of iron ions in cells, lipid peroxidation and the presence of an imbalance between the accumulation of reactive oxygen species and antioxidants. Recently, data has begun to accumulate on the relationship between ferroptosis and numerous diseases such as cancer, Parkinson's disease, osteoarthritis, systemic lupus erythematosus, etc. Due to growing studies, ferroptosis has been found to be closely related to the appearance and development of diabetes mellitus and its complications, as well.

Keywords: ferroptosis, iron, ROS, diabetes mellitus

INTRODUCTION

Iron is a trace element of enormous importance for living organisms. Its metabolism – transport, disposal, and use are complex processes in which many enzymes and other regulatory components are involved. The overaccumulation of iron in cells leads to a cascade of reactions that result in an increase of deadly lipid peroxides, which, integrating into the cell membrane, lead to cell death – ferroptosis (1). Ferroptosis is a newly discovered form of cell death, which is closely related to the high concentration of iron ions in cells, lipid peroxidation and the presence of an imbalance between the accumulation of reactive oxygen species and antioxidants (2). There are a lot of articles in the field that demonstrate the relationship between ferroptosis and numerous diseases, such as colon and breast cancer (3), Parkinson's and Alzheimer's disease (4), including diabetes mellitus (DM) and its complications (5). Ferroptosis in beta cells of the pancreas results in impaired insulin secretion, and ferroptosis in muscle, fat and liver cells leads to insulin resistance (6). Each of these mechanisms ultimately leads to the development of vicious circle and aggravation of DM complications. This article will provide an overview of iron metabolism, the mechanisms and pathways of ferroptosis, as well as the relationship with DM and its complications.

1. Iron:

1.1 Function:

Iron is a vital trace element for the body. It is included mainly in the composition of haemoglobin – in its protoporphyrin ring, in myoglobin and in many iron-containing enzymes – cytochromes. Its deficiency, as well as an excess in cells, has significant consequences for the health of the living organism. Therefore, its amount in the body should be maintained within relatively narrow limits: 5.8-34.8 mmol/l. Iron deficiency leads to the development of microcytic hypochromic anaemia with impaired gas transport, insufficient oxygen saturation of the blood, hypoxemia, and tissue hypoxia. Deficiency also poses a risk of obesity (6). In turn, the excess that is the subject of this article presents a danger of developing Alzheimer's and Parkinson's disease (4), DM and its complications (5).

1.2 Metabolism:

The iron necessary for the body is obtained in several different ways. Mainly – through food such as meat, eggs, green foods, as well as after the breakdown of old erythrocytes that have completed their life cycle. Iron, which is

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obtained from plant food, is trivalent (7). After obtaining iron products with food, their main resorption takes place in the duodenum-jejunum zone. On the surface of enterocytes, there is a duodenal cytochrome, which, with the help of ascorbic acid, is responsible for converting trivalent iron into divalent iron. Subsequently, with the assistance of a divalent transporter, which is again situated on the enterocytes, the entry of divalent iron into the interior of the cell occurs. There, iron binds to ferritin. If iron is needed, it is exported through the basement membrane of the enterocyte thanks to the enzyme ferroportin. The divalent iron is then converted back into trivalent iron with the help of hephaestin (8). Trivalent iron binds to the transferrin conveyor, which saturates only 1/3 of its capacity. The remaining 2/3 under normal conditions remain unoccupied and perform the function of a backup transport mechanism. Transferrin then binds to transferrin receptors located on the cell surface of depot organs – liver, spleen, bone marrow. Through receptor-mediated endocytosis, iron enters the cell, transforms to divalent and binds again to ferritin (9) **(Figure 1).** If iron is required, it is removed through ferroportin; in the blood ciruloplasmin helps to convert divalent iron into trivalent iron again. The iron is again attached to transferrin and used for its intended purpose (10).

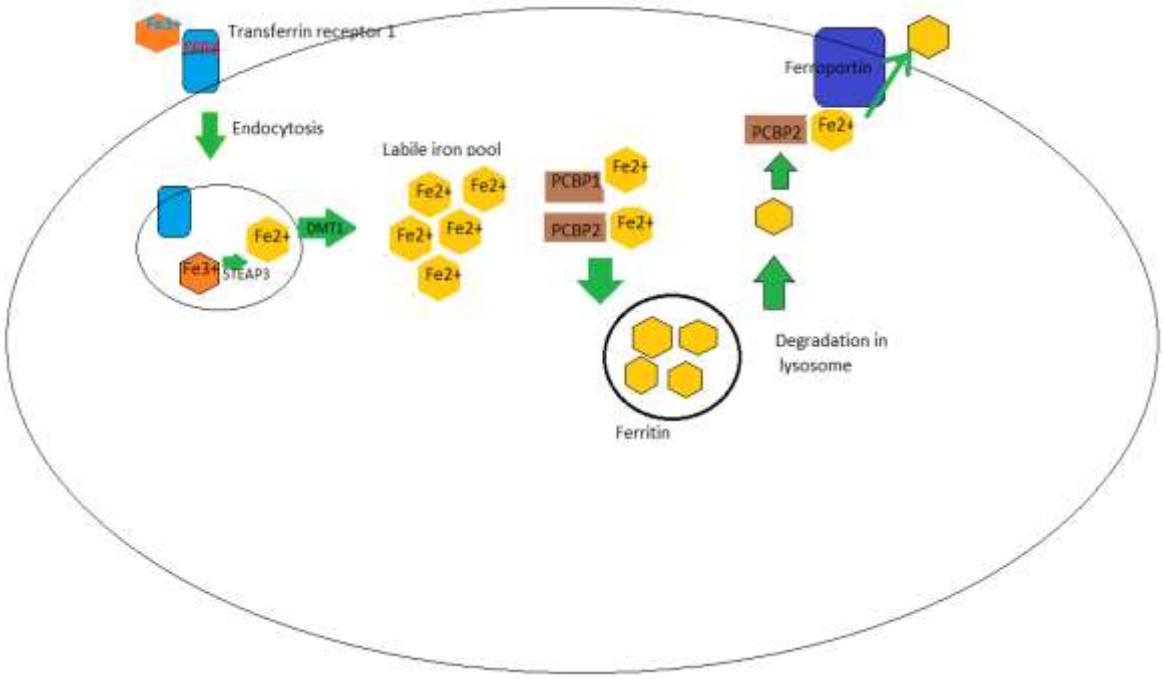

Figure 1. Iron metabolism in the cell. TFR1- Transferrin receptor1; STEAP3 – six-transmembrane epithelial antigen of the prostate 3; DMT1 - divalent metal transporter 1; PCBP1, PCBP2 – Poly(rC)-binding protein 1, Poly(rC)-binding protein 2

Heme iron obtained from meat products enters the cells through heme transporting protein. Once the heme enters the cell in this way, it is broken down by heme oxygenase, after which the resulting iron binds to ferritin and the cycle repeats. After the binding of transferrin to transferrin receptor 1, trivalent iron enters the cell in the composition of the endosome, where, through a protein called STEAP3 (six-transmembrane epithelial antigen of the prostate 3), it is reduced to divalent iron. From the endosome, divalent iron exits into the cytosol via the divalent metal transporter. The iron ions thus entered the cytosol are not bound to a protein and form the cytosolic labile iron pool. The iron from this pool binds to some proteins PCBP1 and PCBP2. If necessary, ferritin degrades, divalent iron is released, which binds again to PCBP2, which carry it to ferroportin (11) **(Figure 1).**

1.3 Iron regulation and ferroptosis:

Ferroptosis could be triggered by multiple factors (6). One of the main mechanisms is due to the accumulation of iron and lipid radicals in the cell (6). Normally, the amount of free unbound iron ions in the cell is small and is regulated by TFR1 and PCBP1, PSBP2 (12). When there is a defect in these proteins, redox-active, non-protein-bound iron accumulates in the cell, giving rise to a cascade of reactions that result in ferroptosis (12).

2. Ferroptosis:

In 2003, Dolma (13). discovered a new compound, erastin, which had a selectively lethal effect on RAS-expressing cancer cells, but the manner of cell death was different from what had been seen before. Yang (14) and Yagoda (15) found that this cell death pattern could be inhibited by iron chelating agents (16). In 2012, Dixon (17) et al. formally named this cell death ferroptosis.

Ferroptosis is obviously different from the other known types of cell death - necrosis, apoptosis, and autophagy in cell morphology and function. Ferroptosis does not have the morphological characteristics that are typical for necrosis, such as swelling of the cytoplasm and organelles and rupture of the cell membrane. Furthermore, it lacks the features associated with conventional cell apoptosis, such as cell shrinkage, chromatin condensation, formation of apoptotic bodies and disintegration of the cytoskeleton. In contrast to autophagy, ferroptosis does not have the formation of classical closed bilayer membrane structures - autophagic vacuoles (16, 18).

From a morphological point of view, ferroptosis can be observed in cells as reduced mitochondrial volume, increased bilayer membrane density and reduction or disappearance of mitochondrial cristae (14, 17); the cell membrane remains intact, and the nucleus is normal in size (16).

A variety of substances that induce ferroptosis can be divided into four categories. One category includes erastin, which is the prototype ferroptosis inducer that reduces glutathione (GSH) levels by directly inhibiting system Xc-. The second category includes RSL3 and DPI7, which directly inhibit GPX4 activity inducing ferroptosis. The third category includes FIN56, which has two methods of triggering ferroptosis. First, FIN56 promotes GPX4 degradation. Second, FIN56 binds to the enzyme squalene synthase, which leads to the depletion of endogenous antioxidant coenzyme Q10 (CoQ10). The final category includes FINO2, an organic peroxide with many features in common with artemisinin, which causes ferroptosis due to a combined effect of the direct oxidation of labile iron and the inactivation of GPX4 (16, 19).

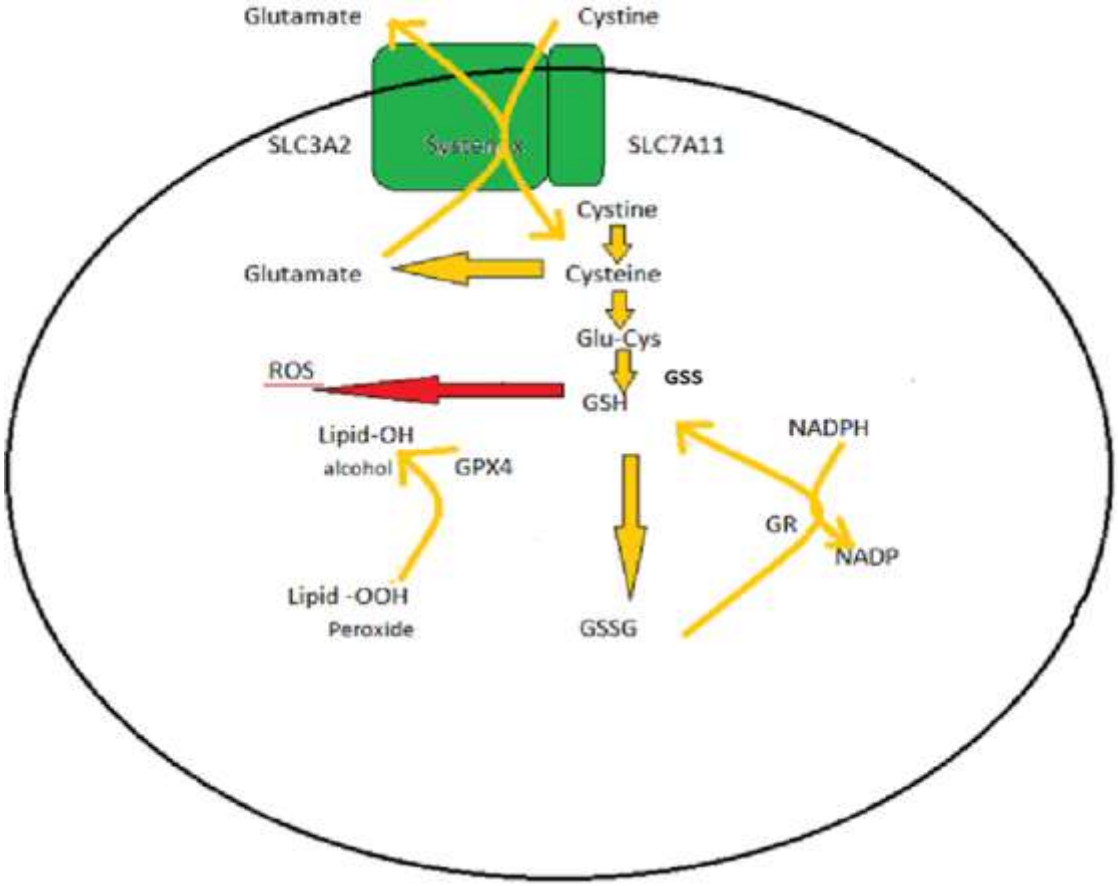

Figure 2. Glutathione synthesis. SLC3A2 - solute carrier family 3 member 2; SLC7A11 - solute carrier family 7 member 11; Glu-Cys - glutamate-cysteine; GSH – Reduced Glutathione; GPX4 – Glutathione peroxidadse; GSSG – Glutathione disulfide - oxidized form of glutathione; GR – Gltathione reductase, GSS – Glutathione syntethase, ROS – Reactive oxygen Species

For the process of ferroptosis, the main importance is the balance between the antioxidant system, in particular the axis gluthatione/glutathione peroxidase 4 (GPX 4), and the production of reactive oxygen species (ROS). In this regard, the synthesis of GSH is of primary significance. Under normal conditions, a two-component transporter amino acid anti-transporter system Xc^- is located along the cell membrane wall, consisting of two subunits: SLC3A2 and SLC7A11 (20). Thanks to the transporter, one molecule of cystine enters the cell, and a molecule of glutamate comes out **(Figure 2).** In the cell, cystine is reduced to cysteine, and this in turn is metabolized by gamma-glutamylcysteine synthetase to γ-glutamylcysteine. The last product, with the help of glycine and glutathione synthetase is transformed into reduced glutathione - GSH, which is an extremely potent antioxidant that manages to neutralize a significant amount of ROS. Glutathione peroxidase 4 (GPX4) utilizes GSH as a cofactor to reduce harmful hydroperoxides. During this process, GSH undergoes oxidation to form its disulfide variant, GSSG **(Figure 2).** GPX4 has a critical role in metabolizing lipid peroxides into lipid alcohol (21). This process is impossible in the accumulation of ROS, which engage GSH. The oxidized glutathione is regenerated with the help of glutathione reductase and the NADPH - NADP reaction **(Figure 2).** Lipid peroxides, in turn, are formed by enzymatic reactions (lipoxygenases, cyclooxygenases and P450) and reactions in which iron is involved, and the Fenton reaction is of great importance (22). Polyunsaturated fatty acids with the help of ACSL4, LPCAT3 are converted to polyunsaturated fatty acids (PUFAs) – phosphatidylethanolamine (PE), which is a metabolite from which lipid peroxides are formed with the help of the enzyme lipoxygenase unbound iron ions as a cofactor (22). At the same time, iron ions through the Fenton reaction and hydrogen peroxide lead to an increase in hydroxyl radicals, which utilize the GSH, which no longer has the ability to participate in the metabolization of lipid peroxides to alcohol peroxides (23). At the same time, ROS support the conversion of PUFAs-PE to lipid peroxides. Lipid peroxides continue to accumulate in the cell, because due to the high presence of ROS, there is no longer a possibility of GPX4 action (24). Already formed, lipid peroxides initiate lipid peroxidation, which is a series of reactions leading to oxidative degradation of the lipid membrane. As a result of this oxidative degradation, there is a disturbance in the semi-permeability function of the membrane, which ultimately leads to cell death called ferroptosis **(Figure 3).**

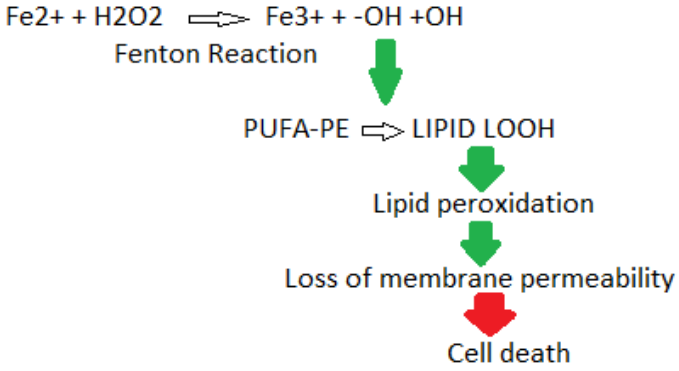

Figure 3. Activation of ferroptosis by iron excess. PUFA-PE - phosphatidylethanolamine contains polyunsaturated fatty acids; LIPID LOOH - Lipid hydroperoxide.

3. Ferroptosis and Diabetes mellitus:

Diabetes mellitus (DM) is a chronic disease with hyperglycaemia due to absolute or relative insulin deficiency (21). Type 1 DM is due to complete destruction of beta cells of the Langerhans islets in the pancreas, while type 2 DM is associated with a defect in insulin secretion and utilization due to long-term insulin resistance (25, 26). It is estimated that the number of cases in 2050 will reach 1.31 billion worldwide (27). DM is a serious socially significant disease mainly because of its late complications, which are microvascular– diabetic nephropathy, diabetic retinopathy, diabetic cardiopathy, encephalopathy and macrovascular (26).

There is a lot of evidence for the relationship between excessive accumulation of iron in cells

and the development of DM (28). Patients suffering from diseases related to the generation of iron excess such as beta thalassemia, microspherocytic anaemia, hereditary hemochromatosis (29, 30), nonalcoholic fatty liver disease (31-33) are at high risk for developing DM. Proof of the connection is the fact that in patients suffering from type 2 DM there are increased levels of ferritin, indicating its increased concentration in cells (28, 34). However, the use of ferritin as a marker of this nature is controversial, since it could also be increased in other conditions, for example, various inflammatory reactions, although that can be corrected by testing C-reactive protein for acute inflammation (34). There are studies done on obese children that show high levels of hepcidin, indicating the accumulation of inflammatory cytokines (35).

One of the main factors for a defect in the insulin-secreting response of beta cells is oxidative stress due to excess iron (6). Beta cells are prone to ferroptosis by several mechanisms (30). Also, the high sensitivity of beta cells to oxidation is not only due to the high concentration of iron accumulation. There is evidence that hyperglycaemia itself increases oxidative stress in insulin-producing pancreatic cells (6). Iron deficiency or excess can affect glucose metabolism, and conversely, hyperglycaemia can lead to iron overload. This close relationship between iron and glucose levels is exemplified by the link between elevated ferritin levels and the development of type 2 DM (26, 35, 36). The harmful effects of iron overload were initially identified in pathological conditions of excess iron, such as hereditary hemochromatosis, characterized by the presence of several elements, including DM, hepatic steatosis, and cardiomyopathy (30). Impaired glucose homeostasis arises from a defect in insulin secretion caused by dysfunction of pancreatic beta cells caused by iron overload, which can be mitigated by phlebotomy or iron chelation (21). Iron metabolism and ferroptosis play a role in glucose homeostasis, affecting both insulin secretion and resistance. At the level of beta cells of the pancreas, iron is involved in the secretion of insulin (37).

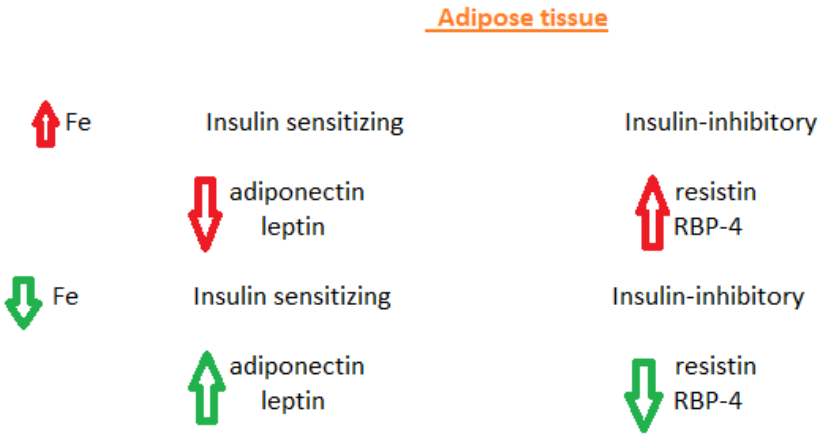

Figure 4. The conection between iron concentration insulin-concentration and adipose tissue. RBP-4 - Retinol binding protein 4.

It is also important to mention the relationship between iron concentration, glucose metabolism and adipose tissue, which is important for modulating glucose metabolism by altering the synthesis of insulin-regulatory adipokines (35) **(Figure 4).** The iron accumulated in adipose tissue regulates glucose metabolism by inducing the expression of the insulin-inhibitory adipokines resistin (38) and RBP-4 (Retinol binding protein 4) (39), thus establishing insulin resistance (35). It has also been found that iron has a role in inhibiting the expression of insulin-sensitizing leptin (40), which reduces insulin sensitivity. In addition, iron overload suppresses adiponectin, which is another insulin-sensitizing adipokine (41).

The iron metabolism takes place in the beta cells of the pancreas in the already familiar way. Circulating iron exists primarily as Fe^{3+}, which is introduced into cells through transferrin. The transferrin receptor (TfR1) mediates iron endocytosis and transferrin in clathrin-coated vesicles. After endocytosis, Fe^{3+} is reduced to

Fe^{2+} in lysosomes. Subsequently, the zinc-iron regulatory family of proteins 8/14 (ZIP8/14) and divalent metal transporter 1 (DMT1) release the oxidized form of iron into the labile iron pool (21). As explained previously, excessive levels of Fe^{2+} promote the production of ROS through the Fenton reaction, enhancing lipid peroxidation and subsequently triggering the initiation of ferroptosis. The induction of ferroptosis then emerges as a factor favouring the pathogenesis of DM through several actions, which are discussed below. Inside the cell, iron is involved in the insulin secretion mechanism by promoting the production of ROS through the Fenton response, which is considered an amplifying signal for insulin secretion (42). Iron overload can lead to pancreatic beta cell insufficiency and apoptosis through several mechanisms, such as ROS generation, reduced capacity of detoxification enzymes, or improved amylin ß-sheet formation, resulting in aggregate deposition (12, 21). Additionally, iron serves as a cofactor for various enzymes and plays an important role in the formation of Fe-S clusters, affecting beta cell proliferation, differentiation, and insulin secretion (43). Ferroptosis is implicated in beta cell function and survival of the pancreas. These cells have low levels of expression of several antioxidant enzymes, such as catalase, GPX4, and superoxide dismutase, which can predispose them to ROS accumulation and therefore ferroptosis induction (24). On one side, in vitro studies have shown that erastin, an inducer of ferroptosis, reduces glucose-induced insulin secretion (GSIS) (24). Conversely, ferrostatin-1, a ferroptosis inhibitor, exhibits protective effects on GSIS ability (24). The death of pancreatic beta cells is a critical factor in the development and progression of DM, and ferroptosis seems to play a role in this process. In pancreatic beta cells, ferroptosis induction is associated with significantly accelerated cell death. Conversely, inhibition of ferroptosis with ferrostatin-1 has been shown to improve the survival of these cells (24). There are probably additional reasons for the particular sensitivity of beta cells to high iron. Beta cells express high levels of the nonspecific divalent metal transporter 1 (DMT1) (44), required for entry into the cytosol of not only iron but also other metals, including zinc, which beta cells require for insulin packaging in secretory granules (45). Although most cellular iron uptake is mediated by the transferrin receptor, iron can be taken up directly by DMT1. This process would be accentuated in pathologic iron overload with high transferrin saturation and resultant labile or non-transferrin-bound iron (45). DMT1 is also upregulated by inflammatory cytokines, which could further enhance that process (45). Even under normal iron conditions, mouse beta cells lacking DMT1 are protected against damage from inflammatory cytokines in both type 1 and type 2 DM models (6, 46). The accumulated dilute iron eventually forms the pool of labile iron and promotes generation of ROS via the Fenton reaction. Other factors, such as chronic arsenic exposure, can also lead to the development of DM, the mechanism in this case being related to mitochondrial damage and mitochondrial ROS production, resulting in mitochondrial ROS-dependent ferroptosis (12). Although a plausible explanation is the insufficient metallization of mitochondrial proteins, necessary for the oxidation of glucose and the stimulation of insulin secretion, other pathways are also involved. Leibold et al. (43), for example, showed that the loss of the iron-regulatory protein IRP-2 leads to functional iron deficiency in beta cells. This, in turn, leads to insulin deficiency from abnormal processing of transfer RNA (tRNA), which leads to reduced synthesis and processing of proinsulin. Considering the extensive range of cellular processes that depend on and are regulated by iron, many other pathways are likely to be discovered (6).

CONCLUSION

The connection between iron metabolism and glucose homeostasis is significant. Iron plays a main role in glucose homeostasis in organs and cells, such as pancreas beta cells, hepatocytes, adipose tissue, neurons and more. Disorders in iron metabolism lead to alterations in insulin secretion and ultimately result in insulin resistance. After the discovery of ferroptosis the relationship between iron metabolism and type 2 DM and its complications became clearer. Excess levels of free reactive iron cause tissue damage and oxidative cell death. As a dangerous oxidant, iron is subject to strict regulation. Both iron deficiency and excess can be complicated by changes in metabolism, including increased risk of DM. These changes are manifest in multiple tissues and through multiple mechanisms. Although most of these mechanisms remain not entirely comprehended, the relationship between ferroptosis and various pathological conditions plays a crucial role in fully understanding their complications.

Consequently, the discovery of the entire role of ferroptosis in these processes will allow better prevention and treatment of many diseases.

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