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Review

Targeting Ferroptosis: New Insights and Therapeutic Advances in MAFLD Complicating T2DM

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Abstract

Epidemiological data show a strong connection between type 2 diabetes mellitus (T2DM) and metabolic-associated fatty liver disease (MAFLD). In recent years, the prevalence of both conditions has been rising simultaneously. When T2DM and MAFLD occur together, patients face a significantly higher risk of glucose and lipid metabolic disorders, with fatty liver more likely to progress to fibrosis or even malignancy. The underlying mechanisms are complex, involving multiple factors such as inflammatory responses, insulin resistance (IR), and cellular aging. Ferroptosis, a newly identified form of programmed cell death characterized by iron accumulation and lipid peroxidation, plays a crucial role in the development of T2DM and MAFLD, drawing significant attention. Current research suggests that ferroptosis contributes to the progression of these two diseases. However, the exact mechanisms of ferroptosis in T2DM-related MAFLD remain unclear. This review summarizes recent advances in ferroptosis research related to T2DM and MAFLD and highlights several potential therapeutic drugs and compounds targeting ferroptosis, aiming to provide a theoretical basis for their clinical application. Additionally, intracellular iron overload, elevated reactive oxygen species levels, and lipid peroxidation are closely associated with ferroptosis. Studies have shown that certain antidiabetic medications (e.g., metformin, pioglitazone, and liraglutide) may slow the progression of MAFLD by inhibiting ferroptosis. Furthermore, experimental studies targeting FerroTerminator1 (FOT1) have demonstrated promising therapeutic value for MAFLD and insulin resistance, suggesting that targeting ferroptosis could be an effective strategy for treating T2DM-related MAFLD.

Keywords: ferroptosis; iron metabolism; type 2 diabetes mellitus; metabolically associated fatty liver disease; insulin resistance

1. Introduction

Metabolic-associated fatty liver disease (MAFLD) is a disease with steatosis of liver cells as its basic pathological feature. With the progression of the disease, steatohepatitis, fibrosis and even liver cancer may occur, and it has become the most common chronic liver disease in the world [1]. Epidemiological investigation shows that the prevalence of MAFLD is increasing year by year and showing a trend of younger age, and the global prevalence of MAFLD has increased by about 50% in the past three decades [2]. Diabetes mellitus (DM) is a lifelong metabolic disease with multiple causes. Prolonged exposure to high glucose levels and metabolic disorders can lead to an increase in oxidative stress and reactive oxygen species (ROS) levels within the cardiac, hepatic, and other systemic tissues of patients. These factors may subsequently induce cell death, thereby causing organ tissue damage [3,4]. Studies have found that compared with the general population, patients with type 2 diabetes mellitus (T2DM) have a more than 2-fold increased risk of developing MAFLD [5,6]. According to epidemiological surveys, MAFLD exists in more than 25% of adults worldwide, and the prevalence of MAFLD in DM patients is as high as 50%–70% [1,7]. From the perspective of the influence of DM on the systemic system, MAFLD belongs to the liver complication of DM, and a study has shown that T2DM is an important indicator to clinically predict the progression of MAFLD to MAFLD and cirrhosis [8]. In addition, prior research has highlighted that MAFLD is also a significant risk factor for T2DM. Patients with both T2DM and MAFLD may face greater challenges in managing their blood glucose levels, experience more severe lipid metabolism disturbances, and see an acceleration in the progression of diabetes-related organ damage. Furthermore, there exists a complex interplay between these two conditions [9–11]. These conditions are closely linked pathophysiologically, with insulin resistance (IR) and lipid metabolism disorders as the central mechanisms. Hepatic steatosis and inflammation worsen hepatic IR, impairing glucose regulation and promoting T2DM. T2DM's hyperglycemic and hyperinsulinemic state stimulates hepatic lipogenesis and adipose tissue IR, increasing free fatty acid (FFA) flux to the liver. IR drives lipolysis in adipose tissue and hepatic lipid synthesis, leading to systemic lipid

metabolism disorders. Lipotoxicity and its induced inflammation further perpetuate IR and organ dysfunction, creating a vicious cycle between the two diseases [12].

At present, the in-depth exploration of the pathogenesis of T2DM and MAFLD and the search for potential therapeutic targets have become a significant area of focus for global public health in recent years.

Ferroptosis is a newly discovered form of cell death in recent years. Characterized by iron accumulation and lipid peroxidation during the process, this type of cell death is iron-dependent, setting it apart from other modes like apoptosis, autophagy, and pyroptosis [13]. Recent studies have highlighted the connection between ferroptosis and diabetes [14]. Ferroptosis can impair the function of pancreatic β cells, trigger IR, and accelerate diabetes progression [15]. Meanwhile, the disruption of glucose and lipid metabolism, along with oxidative stress caused by diabetes, can promote ferroptosis [16]. This vicious cycle also contributes to the development of diabetes-related diseases, including MAFLD. Therefore, in this review article, we summarize potential therapeutic strategies and methods that target ferroptosis to improve T2DM-associated MAFLD. However, it is worth noting that the current research on ferroptosis in T2DM-related MAFLD remains primarily focused on cell and animal experiments. The precise role it plays in clinical practice, as well as its clinical translational value as a therapeutic target, would benefit greatly from further validation through more high-quality model studies and clinical trials.

2. Ferroptosis and Its Mechanism

2.1 Iron Metabolism in Human

Iron is crucial for maintaining normal human physiological functions, including hemoglobin synthesis for oxygen supply, cell metabolism, DNA repair and synthesis, and regulating immune function by promoting immune cell growth and differentiation [17,18]. The body obtains iron from various sources, including heme iron, non-heme iron from food, and iron ions released from decomposed red blood cells [17].

Under normal conditions, iron ions are primarily used for hemoglobin synthesis, with excess stored as ferritin (FTN) and hemosiderin in the liver and macrophages. When iron demand increases, stored iron is released and distributed to tissues via the membrane transporter ferroportin (FPN) [19,20]. At the systemic level, hepcidin, a protein secreted by hepatocytes, plays a key role. It binds to FPN on the surfaces of intestinal cells, macrophages, and hepatocytes, which leads to their internalization and degradation. This process helps inhibit iron absorption and release. When the body is in an iron-deficient state, hepcidin expression decreases, allowing for enhanced iron transport and absorption [21]. Intracellular iron homeostasis is maintained by the iron-regulatory protein (IRP)-iron response element (IRE) system, which regulates iron metabolism gene expression by binding to conserved mRNA motifs. When intracellular iron is low, the system promotes IRP1 synthesis and inhibits FPN expression, enhancing iron intake. Once cells are iron-saturated, transferrin receptor 1 (TFR1) expression decreases, limiting further iron uptake [18,22].

2.2 Disorder of Iron Homeostasis

Under normal conditions, iron ion storage and transport maintain a dynamic balance for human iron homeostasis [23]. Intracellular iron is stored in labile iron pools (LIP) and FTN [24]. When intracellular iron levels are excessive, this balance is disrupted, FTN degrades via autophagy-lysosomes mediated by nuclear receptor coactivator 4 (NCOA4), releasing Fe^{2+}. Accumulated Fe^{2+} triggers Fenton reactions, producing toxic reactive oxygen species that damage proteins, DNA, and cell membranes, ultimately inducing ferroptosis [25]. Research shows that intracellular FTN levels influence ferroptosis sensitivity. Higher FTN levels reduce the labile iron pool, protecting cells from ferroptosis; conversely, lower FTN levels increase the labile iron pool, promoting ferroptosis [26,27]. This occurs because FTN stores iron in an inert form, inhibiting its involvement in oxidative processes. Study also indicates Prominin-2 promotes FTN-containing exosome formation, facilitating iron export and inhibiting ferroptosis [28].

Iron metabolism imbalance serves as the primary trigger of ferroptosis, wherein free iron catalyzes lipid peroxide generation via the Fenton reaction, ultimately inducing cell death. Ferritin, the predominant intracellular iron storage protein, plays a pivotal role in regulating free iron levels and thereby modulating ferroptosis. Ferritin is a multi-subunit protein complex composed of heavy chains (FtH) and light chains (FtL), primarily functioning to sequester free iron and prevent its involvement in oxidative stress reactions. FtH exhibits ferrous oxidase activity, capable of oxidizing Fe^{2+} to Fe^{3+} and storing it within the protein shell, thereby reducing the labile iron pool (LIP) in cells [29]. This storage mechanism not only maintains iron homeostasis but also mitigates ROS production by inhibiting the Fenton reaction, thus protecting cells from oxidative damage [30].

Several studies have highlighted a potential link between ovarian cancer and ferritin. Under non-adherent culture conditions, HEY and PEO1 cells (both are ovarian cancer cell line) upregulate *FtH1* expression to reduce LIP, thereby reducing ROS levels and avoiding ferroptosis. Notably, PEO1 cells exhibit a more pronounced increase in FtH1 expression (8.4-fold) and a more significant reduction in LIP (9-fold), indicating stronger resistance to ferroptosis. When *FtH1* is knocked down, the spheroid formation ability of PEO1 cells is notably impaired, although this does not enhance sensitivity to ferroptosis, this suggests that compensatory antioxidant mechanisms (e.g., glutathione peroxidase 4 (GPX4) or nuclear factor erythroid 2-related factor 2 (NFE2L2) pathways) may be involved. By binding free iron and inhibiting lipid peroxidation, ferritin (particu-

larly FtH) emerges as a critical regulatory node in ferroptosis [31]. However, abnormally elevated ferritin levels may indicate iron overload in tissues. Selective degradation of ferritin through ferritinophagy releases substantial amounts of iron ions, markedly increasing the labile iron pool, which represents a key step in triggering ferroptosis [32]. While ferritin degradation promotes ferroptosis, high ferritin expression may offer protective benefits in certain diseases. Further research is needed to clarify the molecular mechanisms governing dynamic ferritin regulation, paving the way for precise therapies targeting ferroptosis-related conditions.

2.3 Lipid Peroxidation

Lipid peroxidation primarily causes oxidative damage to organelles and plasma membranes through spontaneous lipid oxidation and enzyme catalysis, driving ferroptosis. Polyunsaturated fatty acids (PUFAs) are key substrates in this process [33]. Enzyme-catalyzed lipid peroxidation requires long-chain acetyl-CoA synthetase 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3). These enzymes catalyze the esterification of free PUFAs into phospholipids, leading to their accumulation in cell membranes. Subsequently, lipoxygenase catalyzes membrane disruption, triggering ferroptosis [34].

Current studies show that ACSL4-mediated long-chain fatty acid metabolism is crucial for initiating ferroptosis [35]. Fe^{2+} participates in the Fenton reaction, leading to lipid oxidation and the production of hydroxyl free radicals, which oxidize PUFA-containing phospholipids, causing peroxides and ferroptosis [36]. Research on fibrosarcoma cells treated with four ferroptosis inducers revealed that lipid peroxidation initially accumulates in the endoplasmic reticulum (ER), followed by membrane peroxidation and morphological changes. This indicates the ER is a key target for lipid peroxidation, guiding the development of ferroptosis inhibitors and inducers [37].

2.4 Antioxidant System

Under normal conditions, intracellular lipid peroxides are cleared primarily by the glutathione peroxidase 4/glutathione (GPX4/GSH) axis. GPX4 reduces lipid peroxides to phospholipids using GSH [38]. GSH synthesis depends on System Xc^-, which exchanges extracellular cystine for intracellular glutamate [39,40], Cystine is then reduced to cysteine and incorporated into GSH. Depletion of GSH and inhibition of GPX4 lead to lipid peroxide accumulation, ROS generation, and ferroptosis. The System Xc^-/GSH/GPX4 pathway is a key ferroptosis mechanism [41], Beclin 1 binds to System Xc^- and inhibits its activity, reducing GSH levels and promoting oxidative stress and ferroptosis [42]. P53 suppresses System Xc^- activity by downregulating *SLC7A11*, leading to ferroptosis [43]. In addition, researchers identified an antioxidant pathway involving ferroptosis suppressor protein 1 (FSP1) and coenzyme Q10 (CoQ10). CoQ10 inhibits lipid peroxide formation, while FSP1 reduces CoQ10 to eliminate lipid peroxidation and inhibit ferroptosis [44,45]. It was found that ginsenoside Rg1 activates the FSP1/CoQ10 axis, thereby inhibiting lipopolysaccharide-induced lipid peroxidation in human kidney cell line (HK-2) cells and prevents ferroptosis in renal tubular cells [46,47]. Dihydroorotate dehydrogenase (DHODH), a CoQ10-reducing flavin protein similar to FSP1, inhibits ferroptosis in the mitochondrial membrane and regulates cellular sensitivity to the GPX4 inhibitor RAS selective lethal 3 (RSL3) [48,49].

3. Mechanism of Ferroptosis in T2DM-Associated MAFLD

3.1 Insulin Resistance

IR plays a crucial role in the development of T2DM and MAFLD. Individuals with T2DM often experience peripheral IR, which can result in disorders of glucose and lipid metabolism, this leads to increased fat breakdown, higher levels of FFA, and eventually hepatic steatosis [50]. Current studies show that IR is positively correlated with MAFLD development, liver fibrosis, and can promote hepatocyte steatosis, progressing to MAFLD and liver fibrosis [51]. An increasing number of studies suggest that IR is closely linked to iron overload, and disruptions in iron balance may contribute to the development of IR [52,53] (Fig. 1). High-iron diets may alter insulin signaling in the liver and muscles, resulting in elevated hepatic glucose production in mice with excessive iron levels [53]. Research shows that treating iron overload can help improve IR. A study on animals has found that using iron chelators can make obese models more sensitive to insulin [54].

Iron overload increases intracellular ROS production, which impairs glucose uptake and insulin sensitivity in muscle and fat [55]. Elevated ROS levels cause oxidative stress, contributing to IR pathogenesis, particularly through mitochondrial damage [56]. FFA are also key factors in IR. Palmitic acid (PA) upregulates TFR1, promoting endoplasmic reticulum stress and calcium depletion, leading to iron overload, mitochondrial damage, and increased ROS production. This ultimately reduces insulin sensitivity and causes IR. After knocking out the TFR1 gene, PA failed to induce iron overload and IR in cells, and iron chelating agents significantly reduced PA-induced IR [37,57]. Research shows that increasing mitochondrial NEET protein (mitoNEET) expression regulates iron levels in heart and skeletal muscle cells, reducing harmful ROS production and protecting against iron overload damage [58], iron overload can lead to ferroptosis and IR by inhibiting the janus kinase 2/signal transducer and activator of transcription 3/solute carrier family 7 member 11 (JAK2/STAT3/SLC7A11) pathway. However, the iron chelator deferasirox (DFX) helps reduce glycogen and GSH levels in liver tissue and HepG2 cells, thereby alleviating iron overload-induced IR [59]. Autophagy disorders

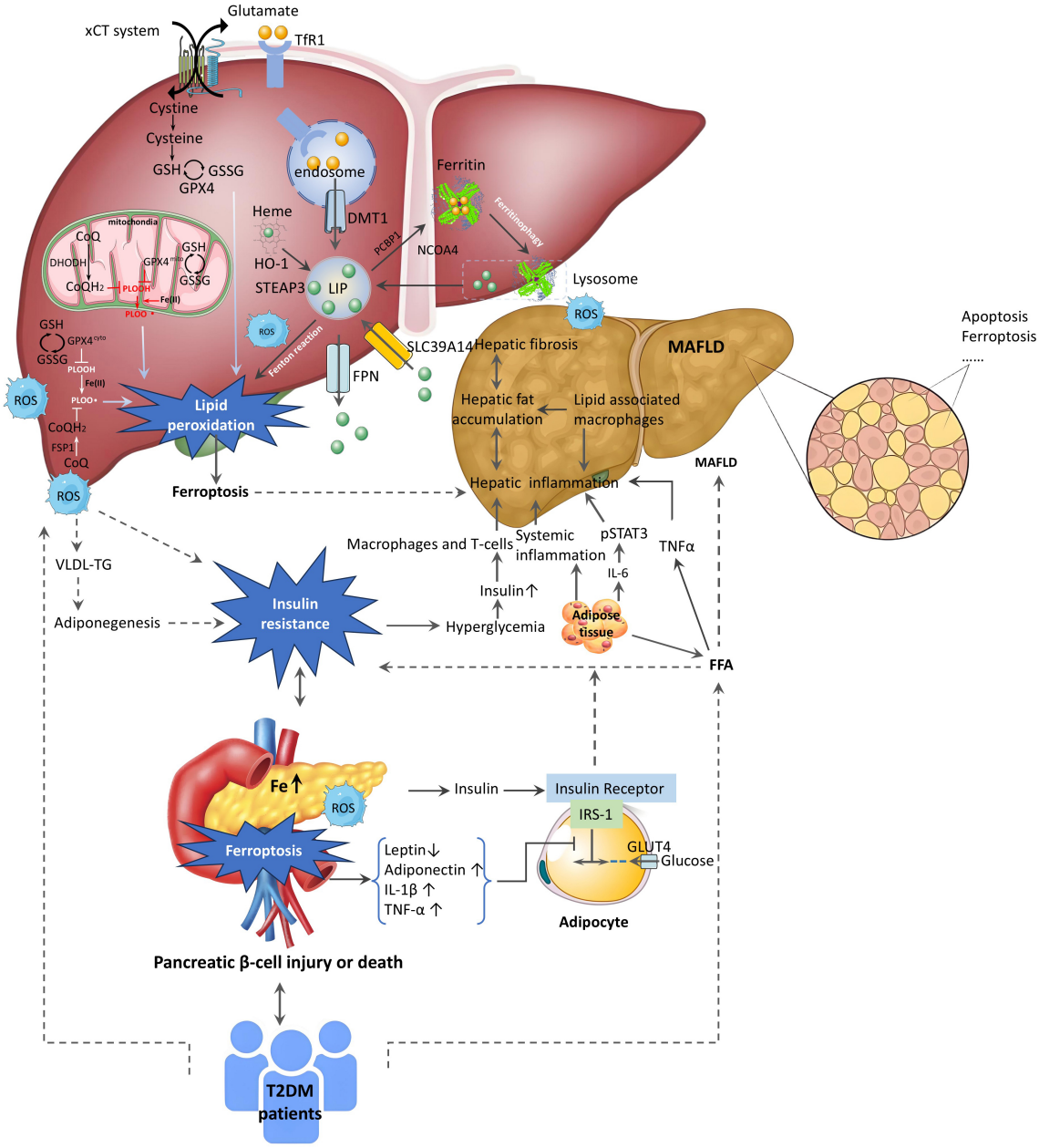

Fig. 1. The regulatory mechanisms of ferroptosis in MAFLD and the relationship between T2DM and the progression of MAFLD. The connection between MAFLD and T2DM is mediated through IR, ROS, and LPO. MAFLD leads to liver steatosis, lipogenic changes, declining function, and inflammation, worsening IR and driving T2DM progression. Elevated FFA levels in MAFLD exacerbate liver IR and fat accumulation. In T2DM, IR increases insulin secretion, intensifying FFA synthesis. Higher hepatic fatty acids cause hepatocyte dysfunction, inflammation, oxidative stress, and accelerate MAFLD development. Inflammation induces oxidative stress, leading to cell death, tissue damage, mitochondrial dysfunction, and excessive FFA accumulation, impairing insulin signaling and sensitivity. The liver regulates glycolipid metabolism and iron storage; recent studies link these functions to ferroptosis. Iron overload damages mitochondria, increases ROS, reduces adiponectin receptor expression, and worsens IR, collectively driving disease progression. ↑ indicates an increase, ↓ denotes a decrease. MAFLD, metabolic-associated fatty liver disease; T2DM, type 2 diabetes mellitus; IR, insulin resistance; ROS, reactive oxygen species; LPO, lipid peroxidation; FFA, free fatty acid; GSH, glutathione; GPX4, glutathione peroxidase 4; HO-1, heme oxygenase-1; STEAP3, six-transmembrane epithelial antigen of the prostate 3; LIP, labile iron pool; FPN, ferroportin; CoQH2, ubiquinol; DMT1, divalent metal transporter 1; PCBP1, poly (Rc) binding protein 1; NCOA4, nuclear receptor coactivator 4; pSTAT3, phosphorylated signal transducer and activator of transcription 3; TNFα, tumor necrosis factor α; IL-6, interleukin-6; IRS-1, insulin receptor substrate 1; GLUT4, glucose transporter 4.

contribute to IR development. Iron overload inhibits the mechanistic target of rapamycin complex 1–UV radiation resistance associated gene (mTORC1-UVRAG) pathway, leading to autophagy defects and promoting IR. Salubrinal, an eukaryotic translation initiation factor 2 subunit alpha (eIF2α) phosphatase inhibitor, enhances autophagy and improves insulin sensitivity in iron-overloaded skeletal muscle cells [60]. High serum ferritin (SF) is a risk factor for diabetes, a recent study shows higher IR incidence in MAFLD patients with liver iron deposition. SF levels correlate positively with IR severity, FerroTerminator1 (FOT1) treatment in MAFLD mouse models reduces SF levels, suggesting SF as a potential prognostic marker for FOT1 treatment of MAFLD [61].

At present, a number of studies have shown that iron overload is closely related to adiponectin. Adiponectin is a protein secreted by adipocytes that can enhance insulin sensitivity and regulate glycolipid metabolism. There is a negative correlation between adiponectin levels and IR. The decreased expression level or signal transduction of this protein can cause impaired insulin signal transduction and glucose tolerance, thereby promoting the occurrence and aggravation of IR [62,63]. Adiponectin requires binding to cell surface receptors to mediate its effects. Increased ROS in iron-overloaded muscle cells causes forkhead box protein O1 (FOXO1) phosphorylation due to oxidative stress, inhibiting adiponectin receptor transcription and reducing receptor expression, leading to adiponectin resistance [64,65]. A Study shows adiponectin restores carnitine palmitoyltransferase 1 (CPT1) activity in gestational diabetes mice, correcting ferroptosis and improving placental damage [66]. Previous research indicates osteocalcin increases adiponectin expression in adipocytes, enhancing insulin sensitivity. Spanish researchers found iron overload decreases circulating osteocalcin levels in cell experiments. Cross-sectional studies confirm a negative correlation between ferritin and osteocalcin/adiponectin levels, suggesting osteocalcin-mediated adiponectin effects on IR may represent a new mechanism [67].

In summary, iron overload contributes to IR via multiple mechanisms, including ROS generation, mitochondrial dysfunction, and inhibition of adiponectin signaling. Conversely, IR may further exacerbate iron overload, thereby establishing a vicious cycle. This interaction represents a critical link between T2DM and MAFLD. Notably, the majority of existing evidence originates from animal models or *in vitro* experiments. Clinical studies that directly demonstrate iron overload as the primary driver of IR and MAFLD progression in T2DM patients, while controlling for confounding factors such as obesity and inflammation, remain scarce. The identification of the osteocalcin-adiponectin-IR axis as a potential novel mechanism is intriguing; however, further in-depth functional investigations and clinical validation are warranted.

3.2 Elevated Ferritin Levels

Ferritin, an essential protein for iron storage, is crucial in diabetes pathophysiology. Study shows higher serum ferritin levels in uncontrolled T2DM individuals, correlating positively with glycated hemoglobin and fasting blood glucose. This suggests iron overload may indicate metabolic disorders in hyperglycemic conditions [68]. Chronic inflammation in diabetes triggers hepcidin production, reducing iron absorption and release, and causing iron accumulation in the liver and pancreas. Ferritin FtH1 expression protects β cells from ferroptosis, while NCOA4-mediated ferritinophagy links ferritin degradation to ferroptosis [32]. At the level of pancreatic β cells, imbalances in iron homeostasis directly impair their function and survival. These cells have low antioxidant enzyme expression, making them vulnerable to oxidative damage. Iron overload not only disrupts β cell mitochondrial function via ROS but also induces β cell death through the ferroptosis pathway [69]. Elevated ferritin levels not only act as a biomarker of iron homeostasis imbalance in diabetes but also contribute significantly to oxidative stress, β cell dysfunction, and the development of complications.

The liver serves as a pivotal organ for glucose and lipid metabolism, as well as iron homeostasis. Serum ferritin acts as the primary protein responsible for iron storage in the liver, and elevated ferritin levels are frequently observed in MAFLD. As a chronic inflammatory condition, MAFLD induces fat-laden hepatocytes and infiltrating immune cells to secrete substantial amounts of pro-inflammatory cytokines. These cytokines subsequently stimulate hepatocytes and macrophages to synthesize and release ferritin, thereby contributing to elevated serum ferritin levels. A cross-sectional study involving 523 patients with T2DM revealed that individuals with hyperferritinemia exhibited significantly higher prevalence rates of MAFLD and non-alcoholic steatohepatitis (NASH) compared to those without hyperferritinemia. After adjusting for age, gender, obesity, and insulin usage, hyperferritinemia persisted as an independent predictor of MAFLD and NASH [70]. Investigations into the relationship between elevated SF levels and T2DM/MAFLD highlight clinical significance; however, the interpretation of SF as an inflammatory marker warrants caution. It remains unclear whether the elevation in SF represents the cause or consequence of iron overload or merely an accompanying phenomenon associated with inflammation.

3.3 Lipid Metabolism Disorders

Owing to insulin insufficiency or resistance, T2DM triggers the mobilization and decomposition of adipose tissue, leading to lipid metabolic disorders and increased FFA production, which are subsequently metabolized and decomposed by the liver [71]. The accumulation of lipids in liver tissues and increased FFA uptake by hepatocytes boost mitochondrial β-oxidation, leading to ROS produc-

tion, ferroptosis, inflammation, cell damage, and the progression of hepatocyte steatosis and MAFLD [72]. Research shows that the BGN4 component of Bifidobacterium bifidum alleviates PA-induced liver damage and ferroptosis. These effects can be reversed by increasing sterol regulatory element-binding protein 1 (SREBP1) expression, indicating BGN4 may reduce MAFLD by interacting with SREBP1 [73]. Ferroptosis occurred in all human hepatocellular carcinoma cell line 2 (HepG2) cells treated with palmitic acid (PA). Cell experiments showed that ginkgolide B, via the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, improves MAFLD caused by lipid accumulation [74]. Moreover, the initial stages of MAFLD progression may be triggered by lipid degeneration and toxicity resulting from excess FFA [75]. Korean researchers found that applying the ferroptosis inducer RSL3 decreased GPX4 expression in hepatocytes, accelerating MAFLD. However, using a GPX4 activator and an iron chelating significantly reduced MAFLD severity. This study highlights the crucial role that regulating GPX4 during ferroptosis plays in influencing the progression of MAFLD [76]. In animal models induced by a high-fat diet, it was observed that ferroptosis in hepatocytes can be mitigated by modulating ferroptosis-related pathways such as SLC7A11 and GPX4, improving high-fat diet-induced MAFLD [77]. The evidence indicates that ferroptosis triggered by lipid accumulation is closely linked to the progression of MAFLD, including steatohepatitis, advanced fibrosis, and cirrhosis. Excess FFA induced by T2DM can also induce ferroptosis, accelerating the progression of MAFLD.

3.4 Dysfunction of Liver Cell Metabolism

The liver is a remarkable organ where glycogen synthesis, decomposition, and gluconeogenesis take place, playing a crucial role in maintaining stable glucose levels. As an important iron storage site, the liver synthesizes and secretes hepcidin, which helps regulate circulating iron levels and contributes to the balance of iron metabolism in human bodies [78]. We currently understand that there is a complex relationship between iron overload, T2DM, and MAFLD, where liver cells play a crucial role. In fact, the liver has a high iron content, and iron overload can cause significant damage to it. Iron overload may accelerate MAFLD progression to liver fibrosis and cirrhosis, while, MAFLD can worsen iron overload [79]. Liang and colleagues examined liver iron content in 494 MAFLD patients, finding positive correlation between liver iron accumulation and disease progression. By integrating findings from various mouse models of MAFLD disease, researchers concluded that liver iron accumulation triggers ferroptosis via the c-Myc-ACSL4 pathway, accelerating disease progression [61]. Liver macrophages store iron and drive inflammation in MAFLD. Zhang *et al*. [80] found that neutrophil cytoplasmic factor expression in macrophages induces hepatocyte hepcidin production via phospholipid peroxides, causing macrophage ferroptosis. The loss of iron-laden macrophages leads to an influx of inflammatory cells, worsening liver inflammation and accelerating MAFLD progression [80] (Fig. 1).

Metabolic abnormal iron overload syndrome is characterized by iron overload and MAFLD, both linked to metabolic syndrome and commonly seen in obese individuals and those with T2DM [81]. The iron overload is often caused by an unhealthy diet and worsened by genetic and environmental factors. While a direct causal relationship with metabolic syndrome remains unclear [82], T2DM increases oxidative stress and ROS levels in the liver, causing cell ferroptosis and liver damage, which promotes fatty liver development [83]. At night, gluconeogenesis is more active, and iron regulates the circadian rhythm of liver glucose production. Iron overload inhibits glycogen synthesis, weakens insulin's suppression of gluconeogenesis, and leads to disordered glucose metabolism and elevated glucose levels [84,85]. The finding suggests that iron overload disrupts the circadian rhythm of liver glucose metabolism holds promising clinical significance. However, translating this insight into practical intervention strategies for managing blood glucose fluctuations in T2DM patients remains an area to be further explored and developed.

Iron overload significantly contributes to IR, a common risk factor closely associated with T2DM and MAFLD. Further studies show that IR not only worsens iron overload but also creates a vicious cycle [86]. Similarly, MAFLD and IR interact in a comparable manner, IR causes adipose tissue to release excess FFA into the liver, promoting lipid accumulation and fatty liver formation. In turn, fatty liver impairs insulin signaling via mechanisms like pro-inflammatory factor secretion and excessive ROS production, exacerbating IR [87,88].

4. Drugs Targeting Ferroptosis in MAFLD

Over the past few decades, understanding of MAFLD pathogenesis has raised hopes for effective treatment. To date, only Resmetirom, a selective hepatic thyroxine receptor β inhibitor, is clinically approved for treating MAFLD. Clinical studies have increasingly highlighted the critical mechanisms behind liver iron accumulation and its role in MAFLD. Additionally, research into the molecular regulatory pathways that trigger ferroptosis and accelerate disease progression is gradually being uncovered. Therefore, by reducing iron accumulation and blocking ferroptosis, we may effectively prevent and potentially treat the onset and progression of MAFLD (Fig. 2 and Table 1).

4.1 Metformin

Metformin (MET) serves as the first-line therapy for T2DM, and clinical studies have confirmed its ability to enhance the therapeutic efficacy in MAFLD (Fig. 2). Its effectiveness is linked to its anti-inflammatory, antioxidant properties, and its role in regulating autophagy and necroptosis

Table 1. Drug intervention in ferroptosis in MAFLD and related mechanisms.

Drugs	Types	Targets	Mechanism
Metformin	Biguanides	xCT, GPX4	Upregulate xCT and GPX4, decrease ACSL4, inhibit ferroptosis
Semaglutide	GLP-1RA	Nrf2	Active Nrf2, inhibit lipid peroxidation
Liraglutide	GLP-1RA	Nrf2, AMPK	Active Nrf2 and AMPK, inhibit LPO and ferroptosis
Dulaglutide	GLP-1RA	Nrf2	Upregulate KLB levels
Pioglitazone	Thiazolidinediones	ACSL4	Inhibit ACSL4, inhibit LPO and ferroptosis
Pioglitazone	Thiazolidinediones	mitoNEET	Stabilize mitoNEET, reduce LPO and ferroptosis in hepatocytes
Deferoxamine	Iron chelator	Free iron	Chelate iron, inhibit Fenton reaction
Deferiprone	Iron chelator	Free iron	Chelate iron, inhibit Fenton reaction
Deferasirox	Iron chelator	Free iron	Chelate iron, inhibit iron overload, inhibit ferroptosis
Ferrostatin-1	Antioxidant	PUFA, ROS	Scavenge ROS, inhibit LPO
Trolox	Antioxidant Water-soluble Vitamin E Derivatives	PUFA	Inhibit Lipid peroxidation and ferroptosis
Liproxstatin-1	Ferroptosis inhibitor	ROS, Nrf2, GPX4	Scavenge ROS, upregulate GPX4, active Nrf2, inhibit LPO

*ACSL4, acyl-CoA synthetase long-chain family member 4; AMPK, Adenosine 5′-monophosphate (AMP)-activated protein kinase; xCT, antiporter of cystine and glutamate, system Xc^-; GLP-1RA, glucagon-like peptide-1 receptor agonist; GPX4, glutathione peroxidase 4; LPO, lipid peroxidation; mitoNEET, CDGSH Iron-Sulfur Domain 1; Nrf2, nuclear factor erythroidderived 2-like 2; ROS, reactive oxygen species; PUFA, polyunsaturated fatty acid; MAFLD, Metabolic-associated fatty liver disease; mitoNEET, mitochondrial NEET protein; KLB, klotho beta.

[89,90]. Recent research shows that metformin slows the progression of MAFLD by mediating ferroptosis in hepatocytes. It was found that two ferroptosis inducers triggered ferroptosis in alpha mouse liver 12 (AML12) cells, while metformin improved cell viability and survival rates after intervention [91]. Metformin alleviated palmitic acid (PA)-induced ferroptosis in AML12 cells and T2DM mouse hepatocytes by reducing intracellular iron overload and ROS levels. This study also highlighted that metformin increased antiporter of cystine and glutamate (xCT) and GPX4 levels in hepatocytes, decreased ACSL4 expression, thereby improving MAFLD through regulation of ferroptosis via the xCT/GPX4/ACSL4 axis [91]. Similarly, Studies have found that metformin activates the AMPK pathway, reducing lysosomal degradation of FPN. This increases FPN expression and alleviates iron overload and ferroptosis in liver cells. Metformin also significantly reduced liver weight and transaminase levels in high-fat diet-induced MAFLD mice, improving steatosis, inflammation, and fibrosis, thus preventing MAFLD progression [91,92]. Unfortunately, this study observed that MET increases GPX4 expression in hepatocytes, but the precise mechanism of MET's influence on the ferroptosis pathway remains unclear (Table 1). As a commonly prescribed first-line medication for managing T2DM in clinical practice, metformin is supported by extensive clinical evidence demonstrating its effectiveness in improving MAFLD. The mechanism related to ferroptosis might help explain, at least in part, its protective effects on the liver.

4.2 GLP-1 Drugs

Glucagon-like peptide-1 (GLP-1) is a polypeptide hormone that stimulates insulin secretion and inhibits glucagon release. Its physiological effects are mediated through both receptor-dependent and non-receptor-dependent pathways. The latter involves the mitochondrial function of small molecular fragments of GLP-1. Extensive research has confirmed that various GLP-1 receptor agonists improve fatty liver conditions and are closely associated with ferroptosis [93,94] (Fig. 2). Specifically, studies on semaglutide have demonstrated its ability to inhibit cellular ferroptosis by regulating klotho beta (KLB) expression and subsequently modulating the adenosine monophosphate-activated protein kinase/acetyl-CoA carboxylase/sirtuin 1/nuclear factor erythroid 2 related factor 2 (AMPK/ACC/SIRT1/Nrf2) signaling pathway (Table 1). Similarly, liraglutide and dulaglutide have been shown to significantly upregulate KLB levels [95]. Recent investigations indicate that liraglutide mitigates ferroptosis in hepatocytes via the glycogen synthase kinase 3 beta/nuclear factor erythroid 2-related factor 2 (GSK3β/Nrf2) and mothers against decapentaplegic homolog 1/5/9/hepatic antimicrobial peptide/ferritin heavy chain (SMAD1/5/9/Hepcidin/FtH) pathways [96] (Table 1). In another study [97] focusing on liraglutide and MAFLD, it was found that liraglutide mediates the AMPK/ACC signaling pathway to inhibit ferroptosis. Additionally, in a study involving a T2DM-related MAFLD mouse model induced by a high-fat diet combined with streptozotocin injection, liraglutide intervention improved glucose metabolism, reduced liver damage, and decreased hepatic lipid accumulation. Researchers concluded that liraglutide inhibits ferroptosis in hepatocytes by activating AMPK and promot-

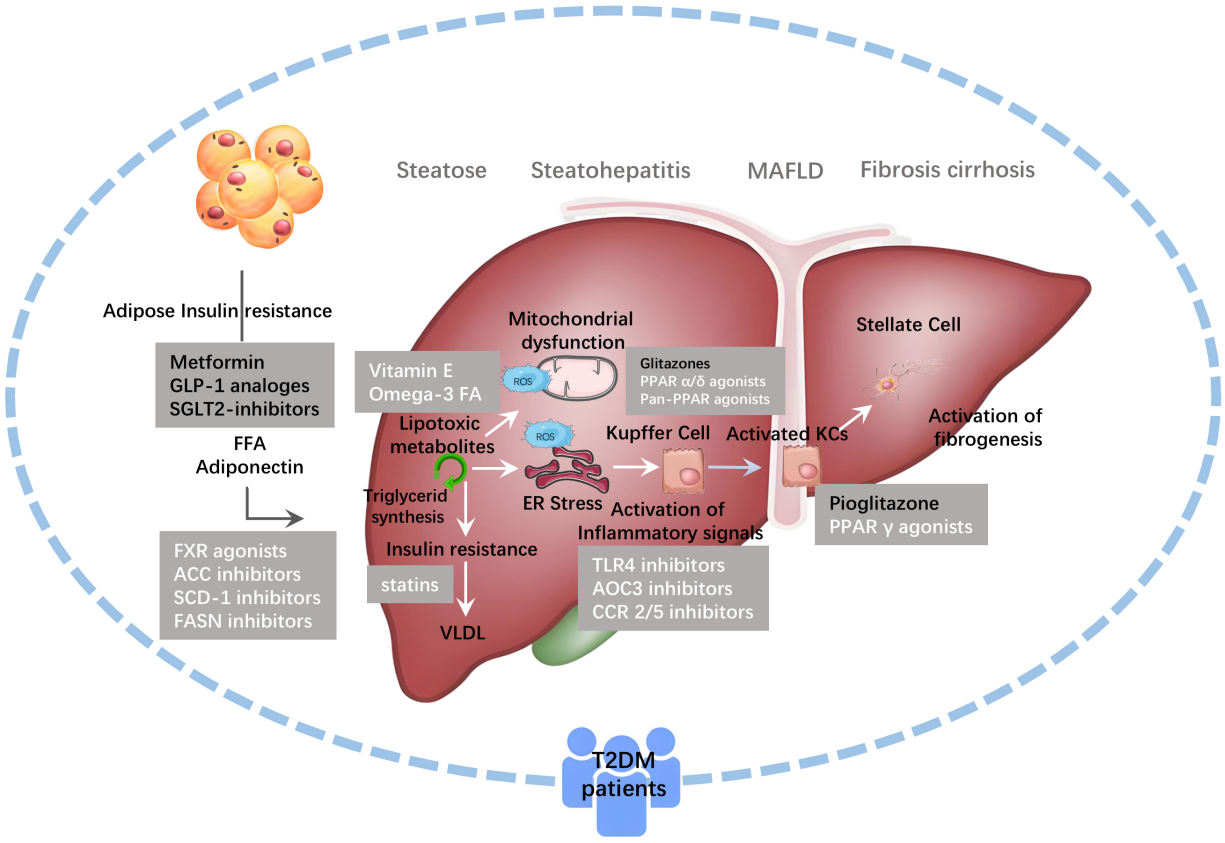

Fig. 2. Drugs Targeting Ferroptosis in MAFLD. The drugs currently used in the clinical treatment of MAFLD/NASH include: nuclear receptor agonists such as farnesoid X receptor (FXR) agonists, peroxisome proliferator-activated receptor (PPAR) agonists, chemokine receptor inhibitors, thyroid hormone receptor-β agonists (Resmetirom), as well as glucagon-like peptide-1 (GLP-1), fibroblast growth factor 21 (FGF 21) or SGLT2 inhibitors, sodium-glucose cotransporter 2 inhibitors, etc. Additionally, several novel drugs for the treatment of MAFLD are currently in various stages of clinical development, with specific focuses on enhancing metabolic function and reducing hepatic fat accumulation, combating inflammation, or inhibiting fibrotic progression. ACC, acetyl-CoA carboxylase; SCD-1, stearoyl-CoA desaturase-1; FASN, fatty acid synthase; VLDL, very-low-density lipoprotein; TLR4, toll-like receptor 4; AOC3, amine oxidase copper containing 3; CCR, C-C chemokine receptor.

ing ACC phosphorylation, an effect that can be blocked by AMPK inhibitors, thereby validating this pathway [97] (Table 1). Tirzepatide (Tilpotide), a novel GLP-1 receptor agonist recently approved by the U.S. Food and Drug Administration for chronic weight management, has shown promising results in clinical multi-center trials (Table 1). These trials revealed that after treatment with tirzepatide, body weight was reduced, along with the liver disease markers fatty liver index and fibrosis-4 (FIB-4) index [98] (Fig. 2). GLP-1 drugs not only contribute to weight and blood sugar management but have also been clinically validated for their significant therapeutic effects on MAFLD, positioning them as a highly promising class of therapeutic agents. While animal studies and in vitro experiments suggest that the inhibition of ferroptosis may play a critical role in their hepatoprotective mechanisms, direct evidence confirming the efficacy of GLP-1 drugs in inhibiting ferroptosis within liver cells of patients with T2DM combined with MAFLD remains insufficient. Considering the association between multiple GLP-1 drugs and ferroptosis, further investigation into the relationship between emerging drugs such as tirzepatide and ferroptosis will undoubtedly represent a pivotal research direction.

4.3 Thiazolidinediones

Thiazolidinediones (TZDs) activate the peroxisome proliferator-activated receptor (PPAR) signaling pathway in adipose tissue, reducing FFA production and hepatic fat accumulation [99] (Table 1). Clinical studies show beneficial effects on liver tissue. A cohort study of 207,367 patients found that TZD therapy helps diabetic patients at risk for MAFLD [100]. Pioglitazone is effective in treating MAFLD, especially in T2DM patients. Randomized controlled trials confirm that pioglitazone reduces hepatocellular steatosis, inflammation, and fibrosis progression [101,102]. Research also indicates that TZDs, including pi-

oglitazone, inhibit ACSL4 expression, thus preventing lipid peroxidation and ferroptosis induced by ferroptosis inducers [103] (Table 1). Moreover, pioglitazone stabilizes mitoNEET expression and mitigates the inhibitory effect of ferroptosis inducers on mitoNEET, reducing lipid peroxidation and ferroptosis in hepatocytes [104] (Table 1). Pioglitazone is associated with risks like weight gain and fluid retention, and it is not approved for MAFLD treatment in non-T2DM patients (Fig. 2). This somewhat limits its broad applicability as an anti-ferroptosis drug for treating MAFLD. Investigating safer and more selective PPARγ modulators might provide a promising approach to address this challenge.

4.4 Iron Chelators

Iron chelating agents play an essential role in clinical settings by helping manage iron overload. These agents work by forming stable complexes with iron ions, which promotes the body's natural ability to excrete excess iron and reduces the overall iron burden. This process helps protect tissues and organs from damage caused by iron overload, such as lipid peroxidation and the production of harmful ROS. Iron chelators are particularly beneficial for patients who require long-term blood transfusions, offering vital support in managing iron levels. Among the currently approved options for clinical use, deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX) stand out as effective treatments [105] (Table 1). Emerging animal studies have revealed that iron chelating agents may help slow the progression of MAFLD and lessen the severity of non-alcoholic steatohepatitis (NASH). As a result, these agents hold considerable promise for treating MAFLD (Fig. 2, Table 1). *In vitro* experiments have shown that DFO significantly reduces iron-induced cell death triggered by PA and alleviates the detrimental effects of iron inducers on hepatocytes. In a NASH mouse model induced by methionine and choline-deficient diet, DFO intervention markedly decreases hepatic iron load, thereby effectively mitigating MAFLD severity. This improvement is evident in several key indicators, such as aminotransferase levels, lipid peroxidation, and GSH levels [76].

Deferrone has shown a remarkable role in the treatment of MAFLD (Fig. 2). In a mouse model of MAFLD induced by a high-fat and high-fructose diet, two weeks of deferrone intervention led to a marked reduction in hepatic iron levels and liver weight. Importantly, deferrone effectively inhibited the elevation of mitochondrial ROS levels. These experimental findings indicate that deferrone can significantly alleviate steatohepatitis symptoms in mice, providing a promising therapeutic option for MAFLD [106] (Table 1).

FerroTerminator1 (FOT1), a novel iron chelator with potent iron removal capabilities, not only effectively inhibits hepatic iron accumulation but also blocks ferroptosis induced by aberrant activation of the c-Myc-ACSL4 signaling pathway. Notably, FOT1 exhibited favorable safety profiles across various toxicity evaluation experiments, laying the groundwork for its future clinical application. Studies have shown that in multiple MAFLD mouse models, long-term FOT1 treatment significantly reduced liver iron levels, improved fibrosis scores, alleviated liver damage, and mitigated systemic IR compared to traditional iron chelators DFO and DFX (Fig. 2, Table 1). Additionally, FOT1 effectively suppressed the expression of genes associated with inflammation and fibrosis, demonstrating that prolonged FOT1 treatment can prevent and mitigate the progression of MAFLD in mice [61] (Table 1). However, the efficacy of iron chelation therapy in preventing and treating MAFLD remains limited to animal models. The long-term use of iron chelators carries a notable risk of causing iron deficiency, which could potentially lead to anemia. As such, it would be valuable to conduct further clinical and translational research to confirm their therapeutic benefits while ensuring patient safety (Fig. 2).

4.5 Antioxidants

As a class of powerful and highly selective inhibitors of ferroptosis, antioxidants can gently protect cells from iron-related lipid peroxidation by reducing the production of ROS and lipid peroxidation products [107,108]. Similar to iron chelating agents, antioxidants have demonstrated significant therapeutic benefits for MAFLD in both animal and cell studies. When the body enters the senescence stage, liver cells face the dual challenge of an increased risk of ferroptosis and heightened lipid toxicity. In a study using a MAFLD senescence mouse model induced by coronary artery disease-high fat (CAD-HFD) diet, it was observed that after intervention with Ferrostatin-1 (Fer1), following the establishment of the MAFLD aging mouse model using a CAD-HFD diet, the expression of ACSL4 in liver cells was significantly reduced, along with a notable decrease in lipid peroxidation levels (Table 1). Importantly, Fer-1 effectively mitigated the adverse effects of aging on these critical parameters and markedly alleviated hepatic steatosis in aged mice. These positive changes made the livers of aged mice more similar to those of young and healthy mice, indicating that Fer-1 prevents MAFLD progression, a disease linked to aging [109] (Fig. 2, Table 1). In a mouse model of MAFLD induced by a high-fat and high-fructose diet, Liproxstatin-1 (Lpt-1) inhibited ferroptosis, reduced hepatic triglycerides and cholesterol, suppressed lipid synthesis and oxidation genes, alleviated IR, decreased mitochondrial ROS, and mitigated liver fibrosis. These findings indicate Lpt-1 effectively ameliorates steatosis and inhibits hepatitis progression in MAFLD mice [110].

Additionally, experimental evidence indicates that Trolox can inhibit ferroptosis in hepatocytes, reduce immune cell infiltration, and lower pro-inflammatory factors expression, improving MAFLD progression in mouse models [111]. Both animal and cellular studies indicate that iron

chelators and antioxidants benefit MAFLD treatment, suggesting that inhibiting ferroptosis could be a promising new target (Table 1). However, practical application will require further drug development and clinical trials.

5. Conclusions

In summary, ferroptosis plays a pivotal role in the pathogenesis of T2DM-associated MAFLD, encompassing intricate interactions among iron overload, IR, elevated ferritin levels, lipid metabolic disorders, and hepatocyte injury. Regarding treatment strategies, commonly prescribed antidiabetic drugs have demonstrated the ability to inhibit ferroptosis, offering novel insights into their hepatoprotective mechanisms. Nevertheless, the critical evidence supporting the central role of ferroptosis primarily stems from cellular and animal studies, and its precise contribution in human T2DM with MAFLD requires confirmation through large-scale population-based studies and clinical trials.

In terms of therapeutic approaches, MET and GLP-1 receptor agonists, due to their well-established clinical profiles and robust efficacy data, currently represent the most promising intervention methods with practical translational potential. Although iron chelators and antioxidants have exhibited substantial effects in animal models, their clinical translation encounters significant challenges: the efficacy and safety of traditional iron chelators for treating non-anemic iron overload in MAFLD remain unclear, with the risk of inducing anemia; FOT1 and other emerging compounds lack human data, and their drugability requires further validation [61]. SF levels serve as crucial biomarkers of ferroptosis and can function as a comprehensive indicator to evaluate metabolic disturbances, inflammatory status, and the severity of liver injury in patients with T2DM and MAFLD. However, these levels should be interpreted in conjunction with inflammatory markers to differentiate between iron overload and inflammatory conditions.

Future research efforts should focus on further validating the role of ferroptosis in human diseases, discovering additional ferroptosis-related biomarkers and clinical testing methods, and exploring innovative, safe, and targeted therapeutic approaches based on the ferroptosis mechanism. By addressing these translational challenges, we can pave the way for targeted ferroptosis inhibition to truly become an effective clinical strategy for managing T2DM-associated MAFLD.

Author Contributions

YS, FY, GW, FN designed the research study. GW, FY, YS, FN wrote the manuscript. YS, GW prepared the figures. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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