REVIEW

Ferroptosis as a potential new therapeutic target for diabetes and its complications

Qian Deng1*, Yue Zhu1*, Mengmeng Zhang1, Aihua Fei2, Jiaqi Liang1, Jinjin Zheng1, Qingping Zhang3, Tong Cheng4 and Xia Ge2

1Graduate College of Anhui University of Chinese Medicine, Hefei, China
2Department of Endocrinology, The Second Affiliated Hospital of Anhui University of Chinese Medicine, Hefei, China
3College of Acupuncture-moxibustion and Tuina, Anhui University of Chinese Medicine, Hefei, China
4Department of Geriatrics, Zhongshan Hospital, Fudan University, Shanghai, China

Correspondence should be addressed to X Ge or Q Zhang or T Cheng: xiage@ahtcm.edu.cn or zqp202202@163.com or chengtong.ct@163.com

* (Q Deng and Y Zhu contributed equally to this work)

Abstract

Diabetes is a complex metabolic disease. In recent years, diabetes and its chronic complications have become a health hotspot of global concern. It is very important to find promising therapeutic targets and directions. Ferroptosis is a new type of programmed cell death that is different from cell necrosis, apoptosis, and autophagy. Ferroptosis is mainly characterized by iron-dependent lipid peroxidation. With the reduction of the anti-oxidative capacity of cells, the accumulated reactive lipid oxygen species will cause oxidative cell death and lead to ferroptosis at lethal levels. Recent studies have shown that ferroptosis plays an important regulatory role in the initiation and development of diabetes, as well as various complications of diabetes. In this review, we will summarize new findings related to ferroptosis and diabetic complications and propose ferroptosis as a potential target for treating diabetic complications.

Introduction

Diabetes is a metabolic disorder which was characterized by hyperglycemia (1), and the prevalence of diabetes and prediabetes in adults around the world has increased in recent decades. Based on the statistic from the International Diabetes Federation, the number of adults with diabetes in the world will reach 537 million in 2021, compared with 2019, the number increased by 16%. Moreover, the adult population with diabetes in the world will reach 783 million by 2045 (2). Persistent hyperglycemia of diabetes is the basis of its chronic complications, multiple organs are involved in it, such as the kidneys, retina, bones and joints, nervous system (peripheral, central), cardiovascular system, etc. (3). Diabetes greatly affects the patient’s health and life quality. Oral hypoglycemic agents and exogenous insulin supplementation are commonly used in the treatment of diabetes, but these treatments only provide temporary glycemic control and cannot prevent effectively the occurrence of diabetic complications. Therefore, more research is urgently needed to explore and discover effective treatment strategies for diabetes and its complications.

As a hot topic, ferroptosis was focused on by many people over the past few years. Ferroptosis was a programmed cell death mode that is unlike other cell death modes (4). In 2003, Brent R Stockwell’s research group at the Whitehead Institute of Biomedical Research investigated the mechanism of small molecule Erastin-induced death of tumor cells with RAS mutation using high-throughput screening of anticancer drugs (5). The study found that this type of cell death was significantly different from other types of cell death at the biochemical, morphological, and genetic levels. This new type of cell death caused by the accumulation of ferrous ions (Fe^{2+})-dependent lipid peroxides was named ferroptosis in 2012...
(4). With the in-depth explorations of new biological molecules involved in the ferroptosis process, the regulatory mechanism of ferroptosis has become more and more complex. Studies indicated that ferroptosis was significantly regulated by pharmacological perturbations of lipid repair systems, including glutathione (GSH), and glutathione peroxidase (GPX4), additionally, ferroptosis was also dependent on a group of active enzymic reactions, such as the biosynthesis of phospholipids (PL) containing polyunsaturated fatty acids, and the selective oxygenation of polyunsaturated fatty acid-phosphatidylethanolamine by lipoxygenase (6, 7, 8).

Moreover, the metabolisms of iron and glucose are closely associated with each other. According to the existing studies, the metabolism of glucose was tightly affected by the deficiency or excess of iron (9), conversely, high glucose (HG) can lead to iron overload, which in turn induces ferroptosis. The main pathological manifestations of diabetes are peripheral insulin resistance and pancreatic islet beta cell failure. The death or dysfunction of pancreatic islet β-cells leads to an absolute or relative insufficient secretion of insulin, which increases blood sugar and leads to diabetes. The studies in pancreatic islet beta cells and proximal renal tubular epithelial cells showed that HG was a causative factor for ferroptosis (10, 11, 12). Hyperglycemia leads to the overproduction of reactive oxygen species (ROS) and subsequently enhances oxidative stress. The increased HG and lipid ROS production, which were closely associated with pancreatic islet beta cell death, are enabling factors for ferroptosis in the diabetic microenvironment (13). Due to the massive production of endogenous ROS and the low expression of antioxidant enzymes, pancreatic islet beta cells are highly susceptible to oxidative stress and prone to ferroptosis. One study showed that the ferroptosis inducer Erastin could significantly reduce the secretion of insulin from pancreatic islet beta cells, while this impaired insulin secretion was significantly rescued by the administration of the ferroptosis inhibitor Ferrostatin-1 (Fer-1) (14). The pieces of evidence earlier suggest that ferroptosis has participated in the processes of pancreatic islet beta cell death and its dysfunction. Furthermore, as an antioxidant transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2) was also significantly associated with the onset and outcome of ferroptosis (13), meanwhile, many ferroptosis-associated molecules, such as the molecules involved in GSH, GPX4, iron (ferritin, transferrin, heme oxygenase), and lipid metabolism, are tightly regulated by Nrf2 (15). The enhanced ferroptosis was observed in the cells with inactivated, inhibited, and deficient Nrf2.

Studies have shown that impaired activation of Nrf2 was significantly associated with the ferroptosis of islet β cells (13). GPX4 is an anti-liperoxidase, a key regulator of ferroptosis, it can reduce complex hydroperoxides to their corresponding counterparts and lipid hydroperoxides (LOOH) to lipid alcohol (LOH), thus interrupting the lipid peroxidation chain reaction (16). The high expression of GPX4 in those insulin-producing cell lines and primary islet cells was observed recently; moreover, depletion of GPX4 also leads to dramatically low cell viability (17). These observations demonstrated that the activation of the Nrf2/GPX4 axis could protect β cells from ferroptosis. Collectively, the occurrence and development of diabetes may be tightly associated with ferroptosis.

Overview of ferroptosis

Ferroptosis is an iron-dependent, nonapoptotic form of cell death. Specifically, it is a result of an imbalance between intracellular lipid ROS generation and degradation. Ferroptosis will be caused when the ROS is accumulated and the antioxidant capacity of cells decreases. Distinct from the features of necrosis, autophagy, and apoptosis, ferroptosis could result in compromised plasma membrane integrity, mild chromatin condensation, cytoplasm and cytoplasmic organelles swelling, increased mitochondrial membrane density, and decreased or absent mitochondrial cristae eventually (4). According to existing studies, many extrinsic or intrinsic pathways could trigger the initiation of ferroptosis. Although more relevant mechanisms of ferroptosis remain unidentified, many biological processes, such as iron metabolism, lipid metabolism, GSH metabolism, mevalonate pathway, NADPH (nicotinamide adenine dinucleotide phosphate)-FSP1 (ferroptosis inhibitory protein 1)-coenzyme Q10 (CoQ10) (18), have significantly participated in the occurrence and execution of ferroptosis. Additionally, deficiency of cysteine and inhibition of GSH synthesis contribute to ferroptosis, and CoQ10 and its reduced form CoQ10-H2, NADPH levels, selenium, and Nrf2 expression are also tightly associated with ferroptosis. Moreover, ferroptosis can be induced by any of these pathways’ impairment. Herein, the underlying mechanisms of ferroptosis will be discussed (Fig. 1).

Iron metabolism

Having a redox property, iron can directly participate in the diffusion of lipid peroxidation and the formation of free radicals. The level of ferritin in the body is directly
related to ferroptosis, and iron plays a crucial role in ferroptosis (4). Circulating iron binds to transferrin (Tf) in the form of ferric iron ($Fe^{3+}$). After introduction into cells via membrane protein transferrin receptor 1 (TFR1), $Fe^{3+}$ is localized to endosomes. In endosomes, due to the acidic environment of endosomes, $Fe^{3+}$ is released from Tf and reduced to ferrous iron ($Fe^{2+}$) by the ferrireductase activity of the six-transmembrane epithelial antigen of the prostate 3. Then, under the regulation of divalent metal transporter 1 (DMT1, also known as SLC11A2), the $Fe^{2+}$ is released from endosomes into the labile iron pool in the cytoplasm, where it is stored in 24 light chains of ferritin (FTL) and 24 heavy chains of ferritin (FTH). Alternatively, through the Fenton reaction, $Fe^{2+}$ and hydrogen peroxide can catalyze the formation of hydroxyl radicals (OH) (19), increase the level of intracellular ROS, and lead to lipid peroxidation. Conversely, excess $Fe^{2+}$ is exported through Ferroportin (FPN), the only known iron-exporting protein, and oxidized to $Fe^{3+}$ by ferroxidase or ceruloplasmin, and then combined with Tf, and finally re-entered into the circulation. A dysfunctional iron homeostasis plays a critical role in ferroptosis.

**Lipid metabolism**

Except for iron, lipid peroxidation and impaired lipid metabolism are other two triggers of ferroptosis (20). Additionally, existing evidence also showed that polyunsaturated fatty acids (PUFA) also play a key role in ferroptosis (21). The studies using Lipidomic analysis revealed that ferroptosis selectively preferentially oxidizes PUFA-containing PL, especially

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**Figure 1**

Three mechanisms of ferroptosis. The regulation mechanism of ferroptosis is mainly related to the regulation of iron metabolism, lipid metabolism, and glutathione metabolism. (ACSL4, acyl-CoA synthetase long-chain family member 4; CP, ceruloplasmin; DMT1, divalent 311 metal transporter 1; FPN, ferroportin; GCL, glutamate cysteine ligase; GPX4, glutathione peroxidase 4; GSH, glutathione; GSS, glutathione synthetase; GSSG, glutathione oxidized; HP, hephaestin; LOX, lipoxygenase; LPCAT3, lysophosphatidylcholine acyltransferase 3; NADPH, nicotinamide adenine dinucleotide phosphate; PL-OOH, phospholipid hydroperoxides; PUFA, polyunsaturated fatty acids; PUFA-CoA, polyunsaturated fatty acyl CoA; PUFA-PL, phospholipid-bound polyunsaturated fatty acids; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; STEAP3, the six-transmembrane epithelial antigen of the prostate 3; TF, transferrin; TFR1, transferrin receptor 1.)

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**References**

phosphatidylethanolamine (PE) containing arachidonic acid or epinephrine arachidonic acid in the plasma membrane (6, 22). Acyl-coenzyme A (CoA) synthase long-chain family member 4 (ACSL4) is a key enzyme in regulating lipid composition and is significantly involved in PUFA-PE biosynthesis and remodeling in cells. In lipid metabolism pathways, free cytoplasmic PUFA-s are bound to CoA by ACSL4, and then PUFA-CoA is incorporated into PL in the plasma membrane by lysophosphatidylcholine acyltransferase 3. Lipoxygenase (Lox) is a nonheme-containing dioxygenase that can catalyze PUFA through its specific peroxidation and may also be an important regulator of ferroptosis. 12/15Lox oxidation of PUFA-PL causes PL hydroperoxide to accumulate on the plasma membrane (23), eventually leading to iron death.

Glutathione metabolism

Under physiological conditions, cells fight against lipid peroxidation using GPX4. As a necessary selenium protein, lipid peroxides (LOOH) could be converted into non-toxic lipids by GPX4 to resist iron- and oxygen-dependent lipid peroxidation (24). GPX4 is the only member of the GPX4 family that can reduce lipid peroxides (LOOH) and plays a significant regulatory role in ferroptosis (25). Furthermore, RSL3-induced cell death was prevented by GPX4 overexpression (26).

GSH is a cofactor of GPX4 and is synthesized from glutamate, glycine, and cysteine. The biosynthesis of GSH requires the uptake of cystine through the cystine/glutamate antiporter system Xc−. GPX4 reduces safely PL hydroperoxides to the corresponding lipid alcohols using two GSH molecules, producing HO and glutathione disulfide as byproducts. Inhibition of the Xc-system results in reduced cystine uptake, cysteine depletion, and a lack of synthetic substrates for GSH, which in turn impairs the function of GPX4 (27), leading to homeostatic imbalance. Additionally, the depletion of GPX4 leads to an increase in intracellular iron, which results in PL hydroperoxide accumulation, thereby disrupting membrane integrity through the ferroptosis pathway.

Ferroptosis in diabetic complications

The discovery of ferroptosis has become a hot topic of research and many new areas of disease progression were revealed in recent years, such as cardiovascular diseases, cancer, neurodegenerative diseases, metabolic diseases, ischemia–reperfusion injury (IRI), and damage to the liver, kidneys, and many more (Fig. 2). Recently, a large number of studies have documented the vital impact of ferroptosis on the development of diabetic complications. Later, we will discuss in detail the key molecular mechanisms of ferroptosis in diabetic complications (Fig. 3).

Diabetic nephropathy

Diabetic nephropathy (DN) is one of the serious microvascular complications of diabetes and the leading cause of end-stage renal disease worldwide (28). Regardless of glycemic control, all diabetic patients will potentially develop DN (29, 30, 31). According to a previous study, DN was potentially associated with ferroptosis (32). Since renal tubules are prone to metabolic disturbance and ischemia, tubular defects may be an important cause of proteinuria in patients with DN (33). Because of the high sensitivity of the renal tubules to lipid peroxidation and oxidative stress (34), frequently occurred ferroptosis of renal tubules was observed in the development of renal disease (35). Meanwhile, ferroptosis-caused tubular damage was also found in patients with diabetes. In comparison to the non-treated control renal tubular cells, the cells with transforming growth factor beta-1 (TGFB1) stimulation exhibited significantly decreased intracellular GSH production and elevated lipid peroxidation. In addition, compared to the normal control samples collected from healthy controls, the renal biopsy samples collected from diabetic patients showed dramatically reduced mRNA expression of the cystine/glutamate antiporter system Xc– (xCT) and GPX4, suggesting the occurrence of ferroptosis (10). Ferroptosis is triggered by the accumulation of lipid peroxide through mechanisms dependent on xCT and GPX4. Meanwhile, the TGFB1-induced ferroptosis could be significantly suppressed by ferroptosis inhibitors in renal tubular cells. Moreover, renal fibrosis can be induced by diabetic tubular cell death and ferroptosis. A previous study reported that increased activation of pro-inflammatory and profibrotic signaling pathways was observed in the renal tubular epithelial cells under HG conditions (36). The results from in vivo experiments have shown that ferroptosis promotes diabetic renal tubular injury in db/db mice through the hypoxia-inducible factor (HIF)-1a/heme oxygenase (HO)-1 pathway (32). The ferroptosis-inducing regulator GPX4 induces acute renal failure in mice when it is inactivated (27). As we know, HG-induced glomerular podocyte injury was considered one of the primary mechanisms of DN.
As an antioxidant enzyme, peroxiredoxin 6 (PRDX6) could negatively regulate the development of ferroptosis. Previous research has demonstrated that the protective effect of PRDX6 is significantly abolished by the treatment of ferroptosis inducer erastin, suggesting the suppressive effect of PRDX6 on ferroptosis and its protective effect on the HG-induced podocyte injury (37). Significant changes in some ferroptosis-associated biomarkers of ferroptosis inducer erastin, suggesting the suppressive effect of PRDX6 on ferroptosis and its protective effect on the HG-induced podocyte injury (37). Significant changes in some ferroptosis-associated biomarkers,
such as increased ACSL4 expression, decreased GPX4 expression, and elevated content of lipid peroxide and iron, were observed in the kidney of the mouse with DN. The ACSL4 inhibitor rosiglitazone can significantly reduce lipid peroxide malondialdehyde and iron content, inhibit inflammation in DN, and thus impair ferroptosis (38). These studies suggest that ferroptosis plays a significant role in the occurrence and development of DN. However, in addition to the reported and explored ferroptosis-related mechanisms, whether there are more regulatory pathways that mediate the occurrence and development of ferroptosis is unclear. We should conduct more studies on the specific mechanisms of ferroptosis to expand our understanding and treatment of DN.

**Diabetic retinopathy**

Diabetic retinopathy (DR) is the most common microvascular complication in people with diabetes and can cause blindness in severe cases (39), and hyperglycemia is a major risk element for DR. Iron overload leads to increased intracellular iron deposition, which in turn leads to irreversible tissue damage and organ failure (40). Ferroptosis is also considered as a programmed cell death which is highly dependent on iron. The increased iron accumulation which was found in the retina of a diabetic mouse model and significantly affects the integrity of the blood–retinal barrier (BRB) and accelerates the damage of retinal cells through enhanced oxidative stress (41). Retinal pigment epithelium cells (RPEs) are located between photoreceptor cells and the choroid of the eye (42). The disruption of the BRB caused by the damage of RPE cells is also significantly associated with DR (43). There are high levels of ROS in RPE cells; however, in normal circumstances, the antioxidant system will remove excess ROS. The alternation of antioxidant system activity which is mainly caused by hyperglycemia increased the RPE cells’ production of ROS in DR, which is considered as the major reason for the loss of RPE cell function. A previous experiment in vitro showed that HG can increase the death of RPE cells by promoting ferroptosis (44). Additionally, the down-regulated Nrf2 expression was observed in RPE cells, and the cell damage caused by HG can be efficiently inhibited through the activation of Nrf2 in DR (45). There is evidence that the ferroptosis inhibitors Fer-1 and deferoxamine could rescue RPE cells from death more effectively than the inhibitors of necroptosis and apoptosis (46). Taken together, ferroptosis plays a major role in the death of RPE cells. Ferroptosis may become a new target for the treatment of DR. However, whether ferroptosis is involved in HG-induced death of other retinal neurons needs further research to prove.

**Diabetic osteoporosis**

Diabetic osteoporosis (DOP) is considered as one of the serious complications of diabetes. Epidemiological surveys have shown that (47) approximately 50–66% of patients will be complicated with osteopenia, and approximately 33% of patients will develop osteoporosis among diabetic patients. DOP is the main cause of fragility fractures and trabecular deterioration in diabetic patients (48). The diabetic microenvironment significantly enhances the ferroptosis of osteocyte ferroptosis in vitro, and thus, loss of osteocyte activity is considered as one of the key pathogenic factors of DOP (49). Through activation of abnormal HO1, a cell-inducible oxidative stress regulator (50), in vitro and in vivo, ferroptosis mediates the death of bone cells and the pathogenesis of DOP in mouse models of DOP. In addition, the usage of ferroptosis inhibitor Fer-1 could effectively rescue the death of osteocytes in DOP (51). The presence of iron overload has been linked with osteoporosis and caused bone loss (52). In a previous study, it was found that the levels of circulating ferritin and serum iron were significantly increased in DOP rats compared to those in normal rats. Meanwhile, the results of immunohistochemistry showed that the expression of solute carrier family 7 member 1 (SLC7A11) and GPX4, two of the main inhibitory proteins of ferroptosis, was significantly decreased, suggesting the existence of ferroptosis in bone tissue of rats with diabetic bone loss. Furthermore, studies have shown that (53, 54) HG could induce ferroptosis in type 2 DOP, through increasing ROS, lipid peroxidation, and depletion of GSH, more importantly, melatonin strengthens bone microstructure, inhibits osteoblast ferroptosis, and enhances the osteogenic capacity of MC3T3-E1 cells in vivo and in vitro by activating Nrf2/HO1 signaling pathways (11). Ferroptosis plays a role in HG-induced DOP through activating the METTL3/ASK1-p38 (methyltransferase-like3/apoptosis signal-regulating kinase 1-p38) signaling pathway, and HG-induced osteoblast ferroptosis may be the major cause of DOP (55). However, more detailed mechanisms still require further study.

**Diabetic cerebrovascular disease**

Diabetic cerebrovascular disease (DCD) refers to cerebrovascular disease induced by diabetes, which mainly includes intracranial microvascular disease and...
showed that the ferroptosis inhibitor Fer-1 could induce myocardial damage and is considered a key factor of obesity and T2DM-related cardiomyopathy development (57). Studies have shown that ferroptosis was the main form of endothelial death in atherosclerotic vascular cell death, and the deficiency of heme oxygenase 1 (HMOX1) could significantly attenuate Fe overload, decrease iron content and ROS level, and subsequently reduce lipid peroxidation, which in turn resulted in reduced ferroptosis in endothelial cells of diabetic patients (58). Recent evidence suggested that ferroptosis may occur during the development and progression of AS, and inhibition of ferroptosis may significantly impair the deterioration of thoracic aortic AS by reducing lipid peroxidation and endothelial dysfunction (59). The Nrf2-Keap1 pathway could reduce AS-related ferroptosis by maintaining cellular iron homeostasis and increasing GSH, NADPH, and GPX4. P53 plays different roles in the ferroptosis of AS at different stages in transcription-dependent and transcription-independent ways (60). Although ferroptosis plays an important role in the occurrence of AS, its relationship with DCD still requires more direct evidence to be proved.

Diabetic cardiomyopathy (DCM) is a major complication and the main cause of death in T2DM patients (61) and is characterized by left ventricular hypertrophy, increased myocardial stiffness, impaired diastolic function, and increased myocardial fibrosis and systolic dysfunction (62). It can be caused by hyperlipidemia, hyperglycemia, over-nourishment, age, heredity, and the environment, among other factors (63). Due to the imbalance of the antioxidant system and the production of excessive ROS, cardiomyocytes will undergo ferroptosis, apoptosis, inflammation, and fibrosis. Palmitic acid (PA), the most common saturated long-chain fatty acid in food, can induce myocardial damage and is considered a key factor of obesity and T2DM-related cardiomyopathy development (64, 65). A recently published study showed that the ferroptosis inhibitor Fer-1 could induce PA-caused hepatocyte death (66). Heat shock factor 1 (HSF1) is a stress-responsive transcription factor that plays a dominant role in the heat shock response (67). HSF1 is induced in various cardiovascular diseases (68) and can protect cardiomyocytes from IRI (69). Accumulated evidence suggested that HSF1 may be involved in the regulation of ferroptosis (70, 71, 72). An interesting experiment demonstrated that ferroptosis was associated with PA-induced cardiomyocyte death, and HSF1 exerted a significant cardioprotective effect on PA-induced cardiomyocyte death by inhibiting ferroptosis (73). The incidence of myocardial ischemia in diabetic patients is 2.45–2.99 times that of non-diabetic patients (74), and cardiomyocyte IRI is more likely to occur in diabetic patients. This increases oxidative stress caused by hyperglycemia and excessive ROS production to some extent (75). Diabetic myocardial IRI is closely associated with endoplasmic reticulum (ER) stress and ROS production (76), and ER stress plays an important role in ferroptosis by inducing unfolded protein response (77). A previous experiment has shown that ferroptosis is associated with the pathological process of diabetic myocardial IRI through the pathway related to ER stress, and inhibition of ferroptosis can alleviate diabetic myocardial IRI (78). However, this experiment only initially confirmed the effect of ferroptosis on ER stress and cardiomyocyte injury, and more research is needed to prove it. Iron homeostasis is critical for the development of cellular ferroptosis (4), and ferroportin 1 (FPN1) plays an important role in iron homeostasis and is the only protein associated with iron release. Nrf2 is a key regulator of antioxidant responses, activating the Nrf2-related pathway could obviously improve the myocardial oxidative damage and cell death, which in turn can alleviate myocardial IRI in Type 1 diabetes (T1DM) patients (79). Additionally, regulation of Nrf2 expression could efficiently protect cardiomyocytes from ferroptosis (80). Due to the controlling of FPN1 transcription by Nrf2, activating the Nrf2/FPN1 pathway can significantly reduce myocardial IRI by regulating ferroptosis and iron homeostasis (81). Fe\(^{2+}\) overload is a culprit in cardiomyocyte ferroptosis and heart failure, demonstrating that iron levels are critical for cardiac homeostasis (82). Endothelial dysfunction is a hallmark of diabetes, meanwhile, endothelial dysfunction is also considered as key and initiating factor in the pathogenesis of cardiovascular complications in diabetes (83). Ferroptosis is found to be related to endothelial dysfunction, and activation of the p53-xCT-GSH axis plays a crucial role in the ferroptosis of endothelial cells.
and endothelial dysfunction (84). Several emerging compounds can be used today to target key ferroptosis regulators to alleviate diabetic myocardial dysfunction. For example, exogenous spermine could attenuate DCM, alleviate oxidative stress, reduce fibrosis, and upregulate myocardial CaSR by blocking the Nrf2–ROS–p53–MuRF1 axis in a diabetic rat model (85). Obeticholic acid can modulate farnesoid X receptor/Nrf2 signaling to inhibit cardiac inflammatory factors and attenuate DCM (86). However, it remains to be investigated whether the protective effects of these compounds are associated with ferroptosis in diabetic cardiomyocytes. At present, most of the evidence on the involvement of ferroptosis in the progress of DCM comes from in vitro studies, and there are relatively few studies on real animal models and clinical studies, so more research evidence is needed to prove the relevance of targeting ferroptosis in the treatment of DCM.

**Influence of ferroptosis inhibition on diabetic complications**

Iron, as a trace element, is necessary for the human body; however, excessive iron could lead to serious damage to the human body, because the abnormal accumulation of iron will generate a large number of free radicals, resulting in damage to DNA, proteins, or other biomolecules (87). Although iron overload has a negative effect on the initiation and progression of DN, the intrinsic mechanism of injury has not been clearly explained. Studies have shown that low-iron diets or iron chelators delay the progression of DN in diabetic rats (88, 89), which provides a new explanation for the pathogenesis of iron overload in this disease. Fer-1, an inhibitor of ferroptosis, can protect multiple organs and tissues from ischemic injury in mouse models and also has protective effects in models of diabetes. Additionally, through activating the PI3K-AKT signaling pathway, Fer-1-mediated inhibition of ferroptosis could significantly reduce inflammation, promote proliferation and migration of vascular endothelial cells and epithelial cells, and improve wound healing (8).

Astragaloside IV (AS-IV) (C41H68O14) is a high-purity natural product extracted from Astragalus membranaceus and has a wide range of pharmacological effects, such as anti-inflammation, antioxidation, immune response enhancement, and anti-stress (90). AS-IV has been shown to inhibit the death of RPE cells during STZ-induced DR by increasing the expression of miR-128, while also inhibiting HG-induced cell damage (91). The latest evidence showed that AS-IV could restore silent information regulator 2-related enzyme 1/Nrf2 activity and the expression of antioxidant-related molecules by inhibiting miR-138-5P expression, thus reducing ferroptosis and inhibiting HG-induced death of RPE cells, suggesting the regulatory function of AS-IV on the RPE cells by ferroptosis suppression and potential therapeutic value of AS-IV for DR treatment (92). Platycodin D (PD) is a triterpenoid saponin with multiple pharmacological properties and has diverse pharmacologic activities, including anti-allergic, anti-inflammatory, and antitumor activities (93). Studies have shown that PD can up-regulate the expression of GPX4 to inhibit HG-induced ferroptosis in HK-2 cells, suggesting that PD may be helpful in the treatment of DN, but more clinical studies are needed to prove it (94). Glabridin is the main ingredient in licorice root, which is often used to improve metabolic abnormalities (such as obesity and diabetes) and has anti-cancer, anti-inflammatory, and other effects (95). Tan et al.’s research showed that GLAB can improve DN in rats, which may be achieved by inhibiting ferroptosis and regulating VEGF/Akt/ERK pathways (96). Resveratrol (RSV) is a natural polyphenol with antioxidant, anti-inflammatory, anti-cancer, anti-aging, anti-diabetic, and protective functions for the heart and nerves (97). A previous study showed that low doses of RSV can reduce blood sugar levels and improve insulin sensitivity in diabetic patients (98). In addition, the protection of low doses of RSV on the acrolein-induced ferroptosis and insulin secretion dysfunction in MIN6 cells through the ER stress-related PERK (Phospho-ERK) signaling pathway was also observed in a published study (99). Sulforaphane, an activator of Nrf2, has been shown to prevent diabetes-induced oxidative stress and cardiac dysfunction (100), and experiments have shown that SFN can inhibit cardiomyocyte ferroptosis in the heart of DCM mice by activating Nrf2, upregulating the levels of ferritin and SLC7A1, and improving DCM in mice (101). Umbelliferone (7-hydroxycoumarin; UMB) is a compound of coumarin, which has antibacterial, antioxidative, antihyperglycemic, and other activities (102), UMB can inhibit HG-induced ferroptosis and oxidative stress by activating the Nrf2/HO1 pathway, thereby preventing renal tubular cell damage and having a protective effect on DN (103). The abovementioned compounds are summarized in Table 1.

There are many drugs that have entered the clinic that can also inhibit the occurrence of ferroptosis, thereby producing a certain effect on diabetic complications.

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Fenofibrate is mostly used to treat hypertriglyceridemia (104). Numerous studies have shown that fenofibrate can improve diabetic complications, but this effect is not dependent on its lipid-lowering ability (105, 106, 107). Studies have shown that by up-regulating Nrf2 expression, fenofibrate treatment also changed the expression of GPX4, SLC7A1, FTH1, TFR1, and other markers related to ferroptosis, which can inhibit diabetes-related ferroptosis, thus delaying the progression of DN (108, 109, 110). Canagliflozin (Cana) is a new sodium-glucose cotransporter 2 inhibitor (SGLT2i) hypoglycemic drug; it can improve diabetic myocardial structure and function, preserve cardiac microvascular barrier function and integrity, sustain eNOS phosphorylation and endothelium-dependent relaxation, as well as improve microvessel density and perfusion (111), and may also reduce the risk of cardiovascular events in people with type 2 diabetes (112). However, the potential mechanism of CANA treatment of DCM still needs to be further explored. Studies have shown that CANA may inhibit ferroptosis by stabilizing cardiac iron steady and inhibiting myocardial oxidative stress, thereby achieving the effect of treating DCM (113). Therefore, CANA may be used as an adjunct to insulin therapy in the process of preventing and treating DCM. N-acetylcysteine (NAC) is an antioxidant that has been used as a drug for nearly 60 years. More and more evidence shows that NAC has a good therapeutic effect in reducing diabetic microvascular complications (114), and NAC is expected to be a drug candidate for the treatment of DN (115). NAC improves ferroptosis by activating the expression of GPX4 through the SITR3-SOD2 pathway, and NAC combined with insulin therapy can effectively improve DN by inhibiting ferroptosis and maintaining mitochondrial redox homeostasis, which suggests that NAC may be used as an adjuvant drug in the treatment of DN (116). Liraglutide is a widely used clinical glucagon-like peptide-1 receptor inhibitor that can be used to treat obesity and diabetes (117). There is evidence that liraglutide can reduce db/db mouse plays a crucial role in ferroptosis in db/db mice (118). Liraglutide attenuates damage to hippocampal neurons and synaptic plasticity and restores cognitive function by inhibiting hippocampal iron death in diabetic cognitive impairment mice (119). All of these compounds and drugs have properties that inhibit ferroptosis; however, their exact targets remain to be further validated.

### Conclusions

Ferroptosis, a novel mode of cell death, is characterized by the accumulation of iron-dependent lipid peroxides and lethal ROS. More and more studies have been conducted on ferroptosis in recent years, but research on ferroptosis still faces challenges, because its exact

### Table 1 Compounds that interfere with ferroptosis to affect diabetes complications.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Function</th>
<th>Possible role in ferroptosis</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Fer-1</td>
<td>Inhibition of TGFβ1 stimulated changes in GSH levels and lipid peroxidation in cultured renal tubular cells, which in turn inhibited ferroptosis.</td>
<td>Inhibitor</td>
<td>(10)</td>
</tr>
<tr>
<td>Exogenous sperm</td>
<td>Block Nrf2-ROS-p35-MuRF1 axis to attenuate DCM.</td>
<td>Inhibitor</td>
<td>(85)</td>
</tr>
<tr>
<td>Quercetin</td>
<td>Certain therapeutic effects on T2DM by inhibiting islet iron deposition and islet β-cell ferroptosis.</td>
<td>Inhibitor</td>
<td>(105)</td>
</tr>
<tr>
<td>Astragaloside IV</td>
<td>Modulates RPE cell function by inhibiting the expression of miR-138-5P, which in turn inhibits ferroptosis.</td>
<td>Inhibitor</td>
<td>(99)</td>
</tr>
<tr>
<td>Platycodin D</td>
<td>Inhibits ferroptosis through up-regulating the expression of GPX4 in HK-2 cells.</td>
<td>Inhibitor</td>
<td>(101)</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Inhibits acrolein-induced ferroptosis in MIN6 cells.</td>
<td>Inhibitor</td>
<td>(102)</td>
</tr>
<tr>
<td>Sulforaphane</td>
<td>Transduction of the NRF2-metallothionein pathway via AMPK/Akt/GSK-3β signaling.</td>
<td>Inhibitor</td>
<td>(103)</td>
</tr>
<tr>
<td>Umbelliferone</td>
<td>Inhibits ferroptosis through activation of the Nrf-2/HO-1 pathway to delay the progression of diabetic nephropathy.</td>
<td>Inhibitor</td>
<td>(108)</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Facilitate Nrf2/p62 signaling to attenuate DCM.</td>
<td>Inhibitor</td>
<td>(106)</td>
</tr>
<tr>
<td>Germacrone</td>
<td>Promotes the treatment of DN by inactivating ferroptosis-dependent mitochondrial damage and podocyte apoptosis.</td>
<td>Inhibitor</td>
<td>(107)</td>
</tr>
<tr>
<td>Cryptochlorogenic</td>
<td>Inhibits ferroptosis in diabetic patients by activating cystine/GPx4/Nrf2 and inhibiting NCOA4.</td>
<td>Inhibitor</td>
<td>(12)</td>
</tr>
<tr>
<td>Glabridin</td>
<td>Inhibits ferroptosis through regulating VEGF/Akt/ERK pathways in DN.</td>
<td>Inhibitor</td>
<td>(103)</td>
</tr>
</tbody>
</table>
mechanism is still being explored and related theories also need further investigations. This article reviewed the three basic regulatory pathways of ferroptosis and the participation of ferroptosis in the development of diabetes and its complications through various pathways, such as the iron metabolism pathway, GPX4, Nrf2, cystine/glutamate antiporter system, Nrf2/FPN1, HIF-1α/HO-1, and so on. Some studies have shown that activating Nrf2 can effectively inhibit the occurrence of ferroptosis, thereby saving cell death and treating diseases, but other studies prevent the emergence of ferroptosis by inhibiting the activation of Nrf2, so we speculate that, whether Nrf2 acts differently on cells under different conditions needs more experiments to prove. Complications of diabetes can affect almost every organ in the body, so it is necessary to continuously explore more effective methods for treatment and therapy. Iron chelators and other ferroptosis inhibitors have shown a good regulatory effect in animal and cell experiments related to diabetes and its complications. The emergence of many natural products and drugs also provides new ideas and new therapeutic targets for the treatment of diabetes and its complications. However, there is growing evidence of crosstalk between ferroptosis and other types of cell death, and it is critical to selectively label ferroptosis-associated cells; therefore, it is necessary to further elucidate this interrelationship in the future, which is a prerequisite for exploring ferroptosis-related mechanisms. At present, many studies are focused on animals or at the molecular level. It is necessary to further improve the research on the pathogenesis of ferroptosis, clarify the specific biomarkers for ferroptosis in clinical research, look for in vivo indicators, and conduct more clinical research as appropriate. The therapeutic effect of ferroptosis inhibitors in diabetic complications also requires further randomized clinical trials to verify. At the same time, finding the marker protein of ferroptosis can also provide new opportunities for subsequent disease diagnosis and therapeutic intervention.

Declaration of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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