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REVIEW

Advances of Iron and Ferroptosis in Diabetic Kidney Disease

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Diabetes mellitus presents a significant threat to human health because it disrupts energy metabolism and gives rise to various complications, including diabetic kidney disease (DKD). Metabolic adaptations occurring in the kidney in response to diabetes contribute to the pathogenesis of DKD. Iron metabolism and ferroptosis, a recently defined form of cell death resulting from iron-dependent excessive accumulation of lipid peroxides, have emerged as crucial players in the progression of DKD. In this comprehensive review, we highlight the profound impact of adaptive and maladaptive responses regulating iron metabolism on the progression of kidney damage in diabetes. We summarize the current understanding of iron homeostasis and ferroptosis in DKD. Finally, we propose that precise manipulation of iron metabolism and ferroptosis may serve as potential strategies for kidney management in diabetes.

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Diabetes mellitus affects approximately 10% of the adult population worldwide (about 529 million estimated in 2021).[1] Although standard of care is established, the chronic effects and long-term complications remain significant public health concerns.[1] DKD, also known as diabetic nephropathy, is one of the most frequently diagnosed complications.[2,3] Approximately half of patients with type 2 diabetes and one-third of patients with type 1 diabetes will develop DKD.[4–6] Moreover, patients with DKD constitute 50% of the end-stage renal disease population, which strongly contributes to the risk of morbidity and mortality.[3] Therefore, the diagnosis and management of DKD are crucial in mitigating the health burden within the diabetes community.

The pathogenesis of DKD is complex, involving glucose metabolism disorders, hemodynamic abnormalities, oxidative stress, genetic predispositions, and inflammation. Recognized as a severe microvascular complication of diabetes mellitus,[4,7,8] DKD is characterized by the activation of the renin-angiotensin-aldosterone system, resulting in the constriction of the efferent arterioles, disrupting self-regulation and causing glomerular hypertension.[9] This ultimately leads to tubulointerstitial fibrosis,[10] tubular atrophy, and expansion of the mesangial cells.[4] In addition, the hyperglycemic and hyperlipidemic environment promotes the production of reactive oxygen species,[11] activation of protein kinase C,[12] and expression of transforming growth factor β-1,[13] leading to oxidative stress and initiating proinflammatory responses[14,15] and oxidative stress.[16,17]

The management strategies for DKD primarily focus on the control of blood glucose, blood pressure, and lipid levels, in addition to diet and lifestyle interventions.[3] Glucose-lowering agents such as metformin and sodium-glucose cotransporter 2 inhibitors have been demonstrating renal protective effects in DKD.[18] In terms of blood pressure control, angiotensin-converting

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enzyme inhibitors or angiotensin receptor blockers have been proven to be renoprotective in DKD.[19] The effects of lipid-lowering agents on kidney function in DKD remain unclear, and there is ongoing debate regarding their mechanisms and outcomes in DKD.[20,21] Antioxidants such as, NADPH oxidases 1/4 inhibitor GKT137831 and ascorbate peroxidase-115 showed potential in alleviating the progress of DKD in several mouse models.[22,23] Nephrologists also recommend strategies beyond medications, including exercise,[24] weight control, specific dietary modification, and macronutrient restriction.[25,26] Patients with DKD often face challenges from other diabetic complications, such as retinopathy, neuropathy, cardiovascular diseases, and foot disease, adding further complexity to DKD management.[3]

Apart from the aforementioned pathologic mechanisms and potential treatments, ferroptosis has become a potential mechanism in the pathogenesis of DKD.[27] It is a type of cell death that can be suppressed by both iron depletion and lipophilic radical-trapping antioxidants; direct detection of lipid peroxidation is also required to validate the occurrence of ferroptosis.[28,29] The evaluation of ferroptosis has been well-developed in the recent decade,[30] including the detection of elevated lipid peroxidation by live cell probe or byproducts, higher labile iron level by ferrous ion (Fe^{2+} probe) staining, shrunken or dense mitochondria morphology via electronic microscope, and specific gene changes such as transferrin receptor 1 (TFR1), etc. However, these methodologies are mostly intrusive, and require extensive time and instruments to accomplish. Other *in situ*, fast, nonintrusive technologies for the evaluation of ferroptosis would be of great interest to basic and clinical research. A recent study highlighted the implication of magnetic resonance imaging (MRI)[31] in iron detection in the kidney of mouse models and patients, which suggested the potential of MRI in detecting iron driven ferroptosis.

Despite emerging research highlighting the significance of ferroptosis in DKD,[32-34] as well as the impact of ferroptosis inhibitors in DKD animal models,[33,35] rigorous assessments of ferroptosis within DKD—or indeed any chronic kidney disease—remain absent, failing to meet the heightened standards established within the domain of ferroptosis research. This review strives to provide a comprehensive analysis of the current knowledge regarding the role of iron and ferroptosis in the pathogenesis of DKD. Our objective is to delineate a clearer trajectory for future investigations and ultimately, facilitate the advancement of the field.

Systemic and Renal Iron Homeostasis

Iron homeostasis is delicately maintained in mammalians (Figure 1).[36] Dietary iron is absorbed by enterocytes in the small intestine.[37,38] In the apical membrane of small intestinal cells, Fe^{3+} is converted to Fe^{2+} by duodenal cytochrome b and transported into the cytoplasm by divalent metal transporter protein 1.[39] Heme, an iron-containing porphyrin, is transported via heme carrier protein 1[40] and/or heme-responsive gene protein 1,[41,42] and then catabolized by heme oxygenase 1 (HO1) to release Fe^{2+}.[43] Cytosolic iron is exported into the blood by the sole iron exporter, ferroportin 1 (FPN1), located at the basolateral membrane of enterocytes.[44] The majority of circulating iron (>90%) is recycled from splenic red pulp macrophages and other tissue-resident macrophages, which phagocytize senescent red blood cells and release iron from hemoglobin or heme, a process known as iron recycling.[45] Circulating iron binds to the carrier protein transferrin (TF) and enters cells through the TF-TFR1 endocytosis system.[46] Recently, a glycoprotein CD44 has been identified to mediate iron, and other metal ion transportation through a hyaluronates-dependent endocytosis system.[47,48] The liver senses fluctuations in iron levels and inflammatory status in the circulation. In response, it synthesizes and secretes hepcidin, a 25–amino acid hormone, to induce internalization and degradation of FPN1,[49] thereby regulating iron uptake and recycling.

Kidneys are known to detect hypoxic conditions and secrete erythropoietin.[50-53] This hormone promotes erythropoiesis in the bone marrow and extramedullary erythropoietic organs.[54] Erythropoietic progenitors produce various erythropoietic factors,[55] including erythroferrone,[56] which interfere with BMP/SMAD signaling in the liver.[57] This leads to suppression of hepcidin expression and increased iron uptake and recycling, adapting to the iron demand for erythropoiesis. In homeostatic conditions,[58] only about 0.1 mg/d of iron is excreted by the kidneys,[59-61] which is relatively low compared to the daily dietary iron uptake from duodenum (approximately 0.95–2.42 mg/d, postulated by 0.95–2.42 mg/d iron loss).[59] This is partly due to the filtering in the glomerulus,[62] whereas other studies indicate that kidney tubules actively reabsorb iron (in the form of TF-bound iron [TBI] and non-TBI) from the filtrate.[58,62,63] This leads to a low urinary iron level (62.4 $\pm$ 4.1 μg/g creatinine) in healthy individuals.[64] The reabsorbed iron is likely exported back to interstitial space or circulation, given that the kidney holds a relatively small iron reservoir compared to the liver and spleen.[65] Nevertheless, the increase of urinary iron in *Hephaestin* and *Ceruloplasmin* double knockout mice[66] and patients with β-thalassaemia major[60,67] suggests a threshold for iron reabsorption and an iron regulatory system in the kidney. This is further supported by the finding that calcium channel blockers significantly

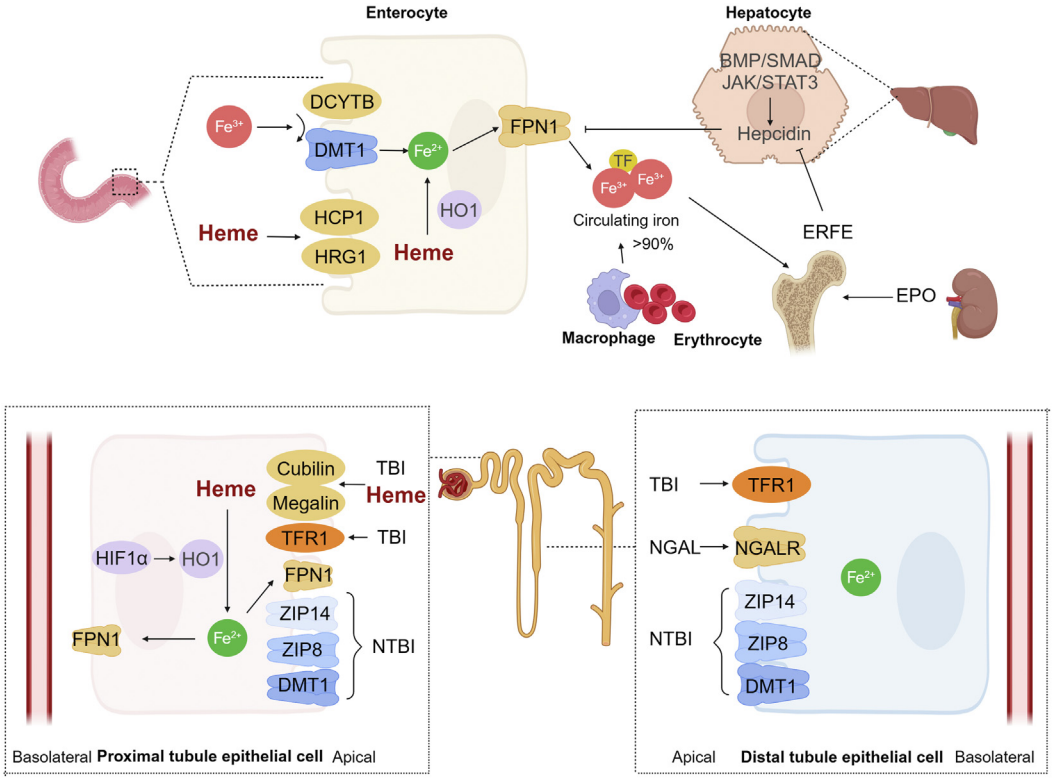

Figure 1. Systemic and renal iron homeostasis. Dietary iron is absorbed at the apical membrane of enterocytes, Fe^{3+} is converted to Fe^{2+} by DCYTB or other metal reductases and transported into the cytoplasm by DMT1. Heme is transported via HCP1 and/or HRG1, and then catabolized by HO1 to release Fe^{2+}. Cytosolic iron is exported into the blood by FPN1 which is located at the basolateral membrane of enterocytes. The majority of circulating iron (>90%) is recycled in macrophages, by engulfing senescent red blood cells. Circulating iron binds to the carrier protein TF. The liver senses fluctuations in iron and inflammation, thereby synthesizes and secretes hepcidin to induce internalization and degradation of FPN1. BMP/SMAD and IL6/STAT3 signaling pathway are 2 of the major pathways maintaining hepcidin transcription. Hypoxia stimulates the kidneys to produce EPO, which enables iron utilization for erythropoiesis in the bone marrow. The hormone ERFE is produced by erythropoietic progenitor cells to inhibit hepcidin synthesis. Proximal and distal tubule epithelial cells reabsorb TBI via TFR1 from the tubular lumen, NTBI is transported into the cytosol by DMT1, zinc transporter ZIP8 and/or ZIP14. Proximal tubule epithelial cells also take up heme and TBI through the megalin/cubilin complex. NGALR locates on distal tubule epithelial cells utilize to bind NGAL as a form of NTBI. HO1 is expressed in proximal tubule epithelial cells driven by HIF1α, to catabolize heme. Proximal tubule epithelial cells expressed FPN1 is more suggested to localize at the basolateral membrane, while some studies showed the apical localization of FPN1. Image was created with BioRender.com. DCYTB, duodenal cytochrome b; DMT1, divalent metal transporter protein 1; EPO, erythropoietin; ERFE, erythroferrone; FPN1, ferroportin 1; HCP1, heme carrier protein 1; HIF1α, hypoxia-inducible factor 1α; HO1, heme oxygenase 1; HRG1, heme-responsive gene protein 1; NGAL, neutrophil gelatinase-associated lipocalin; NGALR, neutrophil gelatinase-associated lipocalin receptor; NTBI, nontransferrin-bound iron; TBI, transferrin-bound iron; TF, transferrin.

enhance urinary iron excretion in the hemochromatosis (HH) mice model.[68,69] Therefore, the kidney represents a potential target for manipulating systemic iron homeostasis.

Various components involved in iron metabolism have been identified in different segments of the kidney. Among these segments, the proximal tubules are particularly equipped for iron reabsorption.[65,70] At the apical membrane of proximal tubules, the TFR1 and megalin/cubilin work together to mediate the uptake of TBI[71,72] and heme iron.[73] The HO1 catalyzes the breakdown of heme into Fe^{2+}, biliverdin, and carbon monoxide.[74-76] Labile iron (Fe^{2+}) undergoes oxidation into Fe^{3+} and is stored within ferritin nanocages in a process called mineralization.[77] The iron exporter, FPN1, is suggested by more studies to be located at the basolateral membrane of proximal tubules,[78-80] although some still argue that the localization might be apical.[70] Cellular iron homeostasis is regulated by iron regulatory protein 1[81] and hypoxia-inducible factor 1 α[82,83] in response to the labile iron pool and hypoxic stress, respectively. Other iron transporters such as neutrophil gelatinase-associated lipocalin receptor, and non-TBI transporters such as Zrt-/Irt-related protein, Zrt-/Irt-related protein 8 and divalent metal transporter protein 1, are also detected in both proximal and distal tubules,[84,85] suggesting an alternative coping system when TBI-mediated iron absorption in the proximal tubules becomes overwhelmed.

Another interesting phenomenon is that iron accumulates in the tubules of the kidney in mouse models of sickle cell diseases,[86] phenylhydrazine-induced

hemolysis,[87] and malaria.[65] This accumulation of iron in the kidney is associated with acute kidney injury and renal dysfunction. It was proposed that the HO1-FTH-FPN1 axis acts as a resolution pathway in response to hemolysis during malaria.[65,88] Deletion of either one among these genes specifically in the proximal tubules of mice leads to exacerbated kidney injury and increased susceptibility to malaria.[65,88] Furthermore, the HO1-FTH-FPN pathway has also been found to be induced in the kidneys from mouse models of rhabdomyolysis[70] and neonatal hemolysis,[89] implying a cytoprotective role of these genes in these conditions involved in heme toxicity.

Several genetically modified animal models of ferroportin provide valuable insights for the working model of renal iron handling. The deletion of *Fpn1* specifically in the distal nephrons and collecting ducts using Ksp-cre does not significantly impact iron deposition in the kidney. However, whole nephron deletion of *Fpn1* driven by Nestin-cre leads to renal iron accumulation specifically in the proximal tubules.[79] This indicates that Fpn1 is involved in the basolateral iron transport in proximal tubule epithelial cells. Dietary iron deficiency intervention further suggests Fpn1 localizes on the basolateral membrane of proximal tubule epithelial cells,[79] because iron deficiency leads to a more severe anemic phenotype and lower iron content in the liver of Nestin-cre; $Fpn1^{fl/fl}$ mice compared to $Fpn1^{fl/fl}$ mice.[79] This is in line with the iron phenotype from *Pax8-creErt2;* $Fpn1^{fl/fl}$ mice and *Pax8-creErt2;* $FpnC326Y^{fl/fl}$ mice, where *Fpn1* is deleted or replaced with a gain-of-function *C326Y* mutant in proximal and distal tubules and in collecting ducts.[90] Moreover, we employed a more specific model, *Pepck-cre;*$Fpn1^{fl/fl}$ mice, where *Fpn1* is deleted in the S3 segment of proximal tubule.[65] Kidney iron is higher at steady state as well as at the peak of *Plasmodium chabaudi* infection in *Pepck-cre;* $Fpn1^{fl/fl}$ mice versus $Fpn1^{fl/fl}$ mice. These genetic findings highlight the unique role of proximal tubules in ferroportin-mediated renal iron reabsorption and storage. Similar protective role of Fpn1 in proximal tubule is validated in folic acid nephrotoxicity.[91]

In summary, the kidney develops its own iron regulatory system to maintain local iron homeostasis and actively participates in systemic iron metabolism, particularly in hypoxic and hemolytic conditions.[58,87,89,92] Proximal tubules appear to be the core segments where most iron components reside, suggesting that they could be a potential target for therapeutic intervention in manipulating kidney iron handling.

Iron in DKD

The established working model of renal iron handling explains the iron dynamics at steady state and hemolytic conditions very well. However, it is crucial to acknowledge that iron redistribution also takes place in various other kidney diseases, including DKD.[31,93] Although the detailed mechanism and clinical significance have not been fully elucidated,[94] numerous studies have indicated a strong correlation between iron accumulation and the development of DKD. As early as the 1990s, nephrologists proposed that iron secretion into urine occurs in patients with DKD.[95] This phenomenon is proposed to be a simultaneous effect of proteinuria. Remarkably, the level of urinary TF excretion positively correlates with tubular iron content, indicating the possibility of its reabsorption through pathways involving TF-TFR1 or megalin/cubilin-mediated endocytosis.[71,72] Consequently, the "leaked" iron may serve as a significant source for intrarenal iron storage and can potentially trigger oxidative damage within the tubules. This is supported by the accumulation of iron in the tubules of diabetic animal models[73,96] and patients with DKD.[93]

However, the exact source of the deposited iron is still in debate. This is because the urinary iron content in patients with DKD is much higher than the amount of urinary TF,[95] suggesting the presence of a non–TF-bound source of iron in the tubular fluid. Potential explanations for this phenomenon include the involvement of heme oxygenase, which releases iron from heme molecules,[43] or the local inflammation and leukocyte infiltration that brings extracellular fluid into the tubules, allowing non-TBI to access tubular cells possibly via transporters such as Zrt-/Irt-related protein/Zrt-/Irt-related protein 8, or divalent metal transporter protein 1.[85,97,98] However, these possibilities have not been thoroughly investigated thus far.

The accumulation of free iron ions promotes the Fenton reaction, leading to excess production of reactive oxygen species and ultimately resulting in iron toxicity.[99] The idea of iron involvement in tissue damage in DKD is supported by findings from human genetics studies. For instance, patients with β-thalassemia have early development and accelerated progress of DKD; this is attributed to their iron loading in parenchyma tissues, including the kidney.[100] A similar situation is reported in patients with HH, who have iron overload in most organs.[101] Up to 60% of patients with HH will develop diabetes,[102,103] which can be corrected for 30% to 40% by phlebotomy or iron chelation.[103,104] Patients with type I HH who carry H63D allelic variant in *HFE* gene have a preference to develop DKD over the healthy population (odds ratio = 1.8).[105] Conversely, treatment with the iron chelator deferiprone or a refined diet (low in iron availability, enriched with polyphenols, and restricted in carbohydrates), has shown improvements in glomerular damage and disease parameters in DKD.[106,107]

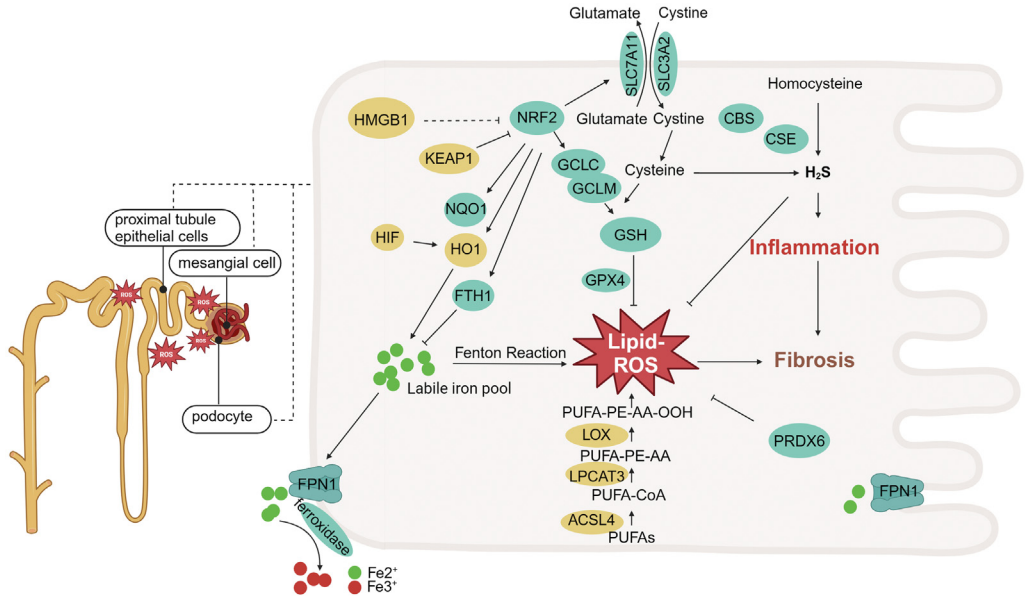

Figure 2. Ferroptosis in diabetic kidney disease. Catalytic iron promotes ROS formation via the Fenton reaction, increasing lipid peroxidation in mesangial cells, podocytes, and especially proximal tubular epithelial cells. This is associated with renal fibrosis. PUFAs are catalyzed by enzymes such as ACSL4, LPCAT3, and LOX, thereby generate oxidized lipids. PRDX6 mitigates lipid peroxidation via suppressing iron accumulation and boosting Gpx4 and Slc7a11 expression. HMGB1 protein blunts DNA repair and antagonizes NRF2. NRF2 sequestered by KEAP1, is activated upon oxidative stress, it potentiates antistress program including NQO1, HO1, and FTH, etc. HIF drives expression of HO1 to catabolize heme, thereby releasing labile iron. Nuclear receptor coactivator 4 and HO1 are the main forces that increase intracellular labile iron. Excessive labile iron (Fe^{2+}) is exported through FPN1 and oxidized into Fe^{3+} by ferroxidases. SLC7A11 and SLC3A2 mediate cystine import; the latter is a substrate of the antioxidant GSH. The rate limiting step of GSH synthesis is catalyzed by GCL, which is composed of GCLC and GCLM subunits, whose expression is promoted by NRF2. GPX4. Image was created with BioRender.com. ACSL4, acyl-CoA synthetase long chain family member 4; FPN1, ferroportin 1; GCL, glutamate cysteine ligase; GPX4, glutathione peroxidase 4; GSH, glutathione; HIF, hypoxia-inducible factor; HMGB1, high-mobility group box 1; HO1, heme oxygenase 1; LOX, lipoxygenases; LPCAT3, lysophosphatidylcholine acyltransferase 3; NRF2, nuclear factor E2 related factor 2; PRDX6, peroxiredoxin 6; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SLC3A2, solute carrier family 3, member 2; SLC7A11, solute carrier family 7 member 11.

Experimental evidence in animal models has demonstrated that mice supplemented with iron[108] or mice with HH[109] exhibit exacerbated oxidative stress and accelerated progression of DKD. When rats were subjected to enforced iron treatment through iron dextran injection, there was an increase in levels of malondialdehyde, protein oxidation, and nitration in the kidney.[108] In a type I HH mouse model (*Hfe*$^{-/-}$ mice), the excessive deposition of iron in the kidney may stimulate the renin-angiotensin system, which is associated with higher levels of kidney injury markers such as kidney injury molecule 1 and Periodic acid-Schiff staining.[109] Conversely, the use of iron chelators or an iron-deficient diet has been shown to alleviate symptoms in animal models of DKD.[96,109-111]

Of note, the cause of DKD in iron overload patients or animal models is still usually considered to be indirect, because pancreatic β cells are hypersensitive to oxidative stress.[112] The iron burden in patients with HH leads to apoptosis in pancreatic islets, which could be a major trigger for insulin insufficiency in diabetes progression.[113] Moreover, hepatic iron overload causes dyslipidemia[114,115] and thereby contributes to nephropathy in diabetes.[116,117] Therefore, whether iron loading in the kidney directly acts on diabetic renal pathology warrants further elucidation. Another consideration is the potential beneficial role of iron in mitigating kidney fibrosis, as indicated by a list of clinical[118,119] and animal researches.[120-124] These studies propose that iron might exert different effects on the pathogenesis of kidney diseases when introduced in a proper way. The cell type in which iron deposits also seems important.[124] Further exploration of iron supplementation in DKD could contribute to unraveling this puzzle.

Ferroptosis in DKD

Iron catalyzed reactive oxygen species formation also drives lipid peroxidation, which leads to ferroptosis.[125,126] In recent years, there has been a surge in mechanistic and clinical studies investigating the relevance of ferroptosis in kidney diseases. Proximal tubule epithelial cells, in particular, are highly sensitive to ferroptosis agonist.[127-129] The well-known genetic ferroptosis model, glutathione peroxidase 4 knockout mice exhibit severe kidney injury in addition to multiple organ failure.[130] In patients and animal models of acute kidney injury[129,131] and DKD,[33,35,132] markers of ferroptosis such as malondialdehyde, 4-hydroxynonenal,

and C11-BODIPY staining are elevated compared to healthy individuals or sham groups. Renal fibrosis has also been proposed as a typical outcome of ferroptosis.[133] These findings suggest that the kidney is a sensitive target for tissue damage mediated by ferroptosis (Figure 2).

Given that iron is accumulated in the renal tubules in patients with DKD[93] animal models[96] and the heightened sensitivity to ferroptosis in the kidney, there is a proposed involvement of ferroptosis as a potential mechanism in the development of DKD.[94] Although clinical evidence is limited due to the relatively recent discovery of this concept, the machinery required for ferroptosis is induced in the kidneys of animal models with both type I and type II diabetes. This is supported by the upregulation of the pro-ferroptotic enzyme acyl-CoA synthetase long chain family member 4 and the downregulation of the ferroptosis suppressors glutathione peroxidase 4, solute carrier family7 member11, and solute carrier family3 member2 in mice exposed to streptozotocin or *db/db* mice, in comparison to control groups.[134] *In vitro* studies have additionally demonstrated the development of ferroptosis in mesangial cells when exposed to erastin (a ferroptosis agonist), along with the increased sensitivity of renal tubular cells to ferroptotic agonists under high glucose conditions.[135] These observations collectively point toward a cellular mechanism of ferroptosis contributing to the pathology in DKD.

The precise initiating signal that triggers ferroptosis in DKD has not been fully characterized. One hypothesis proposes that in the ischemic environment of the diabetic kidney, the hypoxia-inducible factor pathway is upregulated.[136-138] Activation of the hypoxia-inducible factor leads to increased expression of HO1,[139] which in turn enhances the labile iron pool through facilitating the release of iron from hepatic and renal cells.[76] Given the critical role of labile iron in catalyzing lipid peroxidation, this may contribute to tubular damage in DKD. However, thus far, no direct evidence has shown increased labile iron level in renal tubule cells of DKD; however, it is reported that labile iron pool is depleted in kidney macrophages, which contributes to renal fibrosis in chronic kidney disease.[124] This entertains the idea that iron redistribution and cell-cell communication may contribute to ferroptotic damage in kidney diseases, including DKD. Another potential pathway involves the release of iron storage, where nuclear receptor coactivator 4 mediates ferritinophagy and increases cellular labile iron pool through ferritin degradation.[94] Previous studies have demonstrated that knockdown of nuclear receptor coactivator 4 reversed the effect of oxalate-induced ferroptosis in HK-2 cells,[140] and nuclear receptor coactivator 4 expression is elevated in the kidneys of db/db mice.[141] However, nuclear receptor coactivator 4 expression is decreased in most tubule cells from murine single cell transcriptomic analysis[142] and single-nucleus RNA datasets of patients with DKD[143] compared to their controls. Therefore, direct evidence such as tissue-specific knockout model is required to demonstrate the role of nuclear receptor coactivator 4 in DKD.

Aside from iron itself, other pathways have been reported to interact with the ferroptosis cascade. For example, high-mobility group box 1 protein disrupts DNA repair and promotes ferroptosis by counteracting the function of nuclear factor E2 related factor 2,[135] which is known as an important pathway for antioxidation and protection against ferroptosis in DKD.[35,144,145] In addition, the specific protein 1-peroxiredoxin 6 axis has been shown to protect against podocyte injury in DKD by suppressing ferroptosis.[34]

Recent studies have proposed sulfide metabolism as an inhibitory mechanism in controlling ferroptosis.[146,147] This is supported by findings that hydrogen sulfide (H_2S) donors mitigate injury by inhibiting ferroptosis in mouse fibroblasts,[147] acute lung injury, and particulate matter-induced chronic obstructive pulmonary disease.[146] The ferroptosis agonist RSL3 ([1S,3R]-RSL3) blunts cystathionine γ-lyase/H_2S pathway. Conversely, cystathionine γ-lyase expression is upregulated in the presence of the ferroptosis inhibitor, ferrostatin 1.[147] Moreover, H_2S reverses RSL3-induced cell death by preserving mitochondrial structure and lipid metabolism.[147]

Given the cytoprotective potential of sulfide metabolism, it has been characterized to control DKD.[148] The components of sulfide metabolism are widely expressed in the kidneys, and the decrease of enzymes involved in H_2S production (such as cystathionine γ-lyase, cystathionine β-synthase, etc.) and plasma H_2S levels in chronic kidney disease and DKD appears to be a metabolic maladaptation to the renal pathogenesis.[148,149] H_2S, the major product of sulfide metabolism, mitigates DKD through various pathways, including antioxidation, antiinflammation, and antifibrosis.[150] H_2S donors inhibit glomerular basement thickening, mesangial expansion, and interstitial fibrosis in streptozotocin-induced diabetic mice. They also prevent extracellular matrix deposition, preserve vascular compliance, and demonstrate a broad spectrum of targets.[148,151] Mechanistically, H_2S activates the stress-responsive nuclear factor E2 related factor 2 signaling pathway to mitigate oxidative stress induced by high glucose levels.[152,153] H_2S acts by inhibiting transforming growth factor β-1, thereby preventing the accumulation of extracellular matrix, hypertrophy mediated by mesangial cell proliferation, and

ultimately fibrosis by reducing α-smooth muscle actin, fibronectin, and other fibrogenic genes.[154] H_2S also exerts antifibrogenic effects through AMPK activation, which antagonizes the mTOR pathway.[146,155] Furthermore, H_2S reverses the suppressive effect of the matrix metalloproteinase family on fibrogenesis, possibly by promoting miRNA expression.[156] Studies have demonstrated that H_2S blunts nuclear factor κB, and MAPK cascades to prevent the induction of proinflammatory cytokines and cell adhesion molecules in DKD models.[157] Therefore, H_2S or sulfide metabolism can serve as an additional pathway to counteract the pathogenesis of DKD by inhibiting ferroptosis and yielding beneficial effects on oxidative stress, inflammation, and fibrosis.[150,151]

Taken together, iron collaborates with other components in the ferroptosis cascade to trigger deleterious consequences in the kidney. These mechanisms may represent one of the central factors driving the pathogenesis of DKD.

Nonintrusive Method for Renal Iron Determination

Although iron determination is well-developed by current technology, the intrusive procedure for kidney biopsy renders the application of iron assessment a potential early risk factor. Therefore, the development of nonintrusive methods for iron detection or even quantification is appealing. Several studies have demonstrated the superiority of gradient echo T2*-weighted imaging as a noninvasive method for diagnosing iron deposition in the liver, heart, and kidney.[158-162] Although MRI detected renal iron deposition is more reported in hemolytic diseases,[163] MRI has been recently used in detecting renal iron distribution in folic acid–treated mice and kidney transplant patients, this suggested a potential implication of iron-MRI in early diagnosis for kidney diseases.[31] Iron also accumulates in the development and progression of DKD.[31,93,96] Thus, MRI may serve as a valuable clinical tool for identifying renal iron accumulation in DKD.

Technically, in MRI, the paramagnetic nature of hemosiderin and ferritin storage in the kidney leads to a reduction in T2 relaxation time, resulting in signal loss.[164] This diminished signal can be quantified using the parameter R2* (R2* = 1/T2*). Various studies have shown that R2* is proportional to the iron content in the kidney, making it a reliable indicator of relative iron concentration in this tissue.[162,165] In cases of iron-overloaded kidneys, T2-weighted image displays a decrease in signal intensity in the renal cortex, along with lower T2* values and elevated R2* values. Higher R2* values or lower T2* values are indicative of greater iron deposition.[166,167] Nevertheless, various MRI sequences and operating techniques exist, and the choice of MRI examination technique can be tailored to specific clinical requirements.

Concerning kidney injury screening, current functional MRI techniques can be roughly categorized as follows:

1. Blood oxygen level dependent MRI is another T2*-based technique that primarily reflects the renal oxygenation level. It can indirectly indicate the interplay between diabetic kidney injury and iron overload.[168]
2. Susceptibility-weighted imaging leverages the disparity in tissue magnetization rates to generate contrast. As kidney tissue's iron content increases, there is a corresponding reduction in susceptibility-weighted imaging signal intensity. Certain studies propose that susceptibility-weighted imaging surpasses T2-weighted image in assessing susceptibility to excessive iron deposition. Moreover, the amplitude-to-noise ratio calculated from susceptibility-weighted imaging phase images can quantitatively evaluate excessive iron deposition.[169,170]
3. For the detection of mild iron deposition, gradient echo T2*-weighted imaging on a 3.0 Tesla MRI system exhibits greater sensitivity compared to a 1.5 Tesla device. This enables easier differentiation between renal parenchyma and renal sinus. Notably, kidney iron deposition tends to be milder relative to the heart and liver, and measurements conducted with 3.0 Tesla MRI devices yield more accurate information.[171]
4. Diffusion tensor imaging techniques offer quantitative detection of early kidney injury by correlating tissue contrast with T1 and T2 relaxation times and proton density within each pixel. These techniques examine the diffusion correlation of water molecules within the tissue, complementing the effective assessment of iron deposition by MRI.[172]
5. Multiecho Dixon imaging sequences can mitigate the influence of R2* measurements in renal tissue fibrosis or concurrent fat presence.[173]

Although MRI is a powerful tool for delineating iron distribution in renal tissues, present methodologies are unable to differentiate between labile iron pools and the aggregate iron signal (mostly ferritin clusters and hemosiderin iron aggregate) detected by MRI.[160] Consequently, there is an urgent need for technological refinements that enable MRI to specifically identify labile iron, which is more closely associated with the process of ferroptosis.[126] This advancement in MRI technology would significantly enhance its applicability and precision in the context of ferroptosis-related studies.

Conclusion and Perspectives

DKD, as a major microvascular complication of diabetes mellitus, presents a significant burden in terms of morbidity and mortality. The pathophysiology of DKD involves intricate interactions between genetic factors, epigenetic factors, and the environment. However, effectively diagnosing and treating DKD remains a challenge in the field. In this review, we proposed that iron and ferroptosis play a crucial role in DKD pathogenesis, supported by a list of clinical and animal-based studies.

Nevertheless, comprehensive and detailed research is imperative to elucidate the role of ferroptosis in the pathogenesis of DKD, with the ultimate goal of unveiling novel therapeutic avenues for patients with DKD. Moreover, we anticipate that MRI will emerge as a pivotal methodology for advancing the understanding of DKD mechanisms and for developing noninvasive diagnostic strategies. We posit that these scientific advancements will reveal additional precise therapeutic targets, thereby enhancing the treatment of this prevalent and complex condition.

DISCLOSURE

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