

# The Role of Iron Overload in Diabetic Cognitive Impairment: A Review

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**Abstract:** It is well documented that diabetes mellitus (DM) is strongly associated with cognitive decline and structural damage to the brain. Cognitive deficits appear early in DM and continue to worsen as the disease progresses, possibly due to different underlying mechanisms. Normal iron metabolism is necessary to maintain normal physiological functions of the brain, but iron deposition is one of the causes of some neurodegenerative diseases. Increasing evidence shows that iron overload not only increases the risk of DM, but also contributes to the development of cognitive impairment. The current review highlights the role of iron overload in diabetic cognitive impairment (DCI), including the specific location and regulation mechanism of iron deposition in the diabetic brain, the factors that trigger iron deposition, and the consequences of iron deposition. Finally, we also discuss possible therapies to improve DCI and brain iron deposition.

**Keywords:** diabetic cognitive impairment, type 1 diabetes mellitus, type 2 diabetes mellitus, iron overload, iron transport, iron homeostasis

## Introduction

Cognitive impairment is a common complication of diabetes mellitus (DM), manifested in severe deficits in attention, processing speed, learning and memory functions, among others.<sup>1-3</sup> Epidemiological studies estimate that the decline in cognitive function in DM patients is as high as 19% over 20 years.<sup>4</sup> In addition to high complication rates, poorly controlled DM can exacerbate cognitive impairment and may induce neurodegeneration, including Alzheimer's diseases and Parkinson's diseases.<sup>5-7</sup> Thus, further understanding of the molecular targets and pathways leading to cognitive impairment in DM is urgently needed, which is particularly important for the improvement of therapeutic strategies.

As the most abundant transition metal in the human body, iron plays an important role in maintaining normal growth and development, and physiological metabolism. Specifically, iron is involved in important functions such as oxygen transport of hemoglobin, muscle oxygenation of myoglobin, protein synthesis of the mitochondrial respiratory chain, and DNA synthesis of ribonucleotide reductase, also participates in several enzymatic reactions.<sup>8,9</sup>

To note, improperly low or high levels of iron are harmful and lead to a variety of diseases. In fact, previous studies have confirmed a strong association between pathologic iron overload and DM risk,<sup>10</sup> which is mainly reflected in iron deposition -induced oxidative stress/lipid peroxidation, insulin resistance, abnormal glucose and lipid metabolism, and chronic inflammation.<sup>10-15</sup> Iron overload is also associated with many complications of DM,<sup>16-18</sup> including diabetic cognitive impairment (DCI).<sup>19</sup>

As reported, increased iron levels are observed in neurodegenerative diseases.<sup>20,21</sup> Considering that DM promotes and aggravates central nervous system (CNS) injury, iron overload may be an important intermediate target. Therefore, we

reviewed and collated existing evidence with the aim of gaining a clearer understanding of the contribution of iron overload to DCI. The key question is: where and in what cells in the brain does the iron overload occur? What triggers iron overload and what are its ultimate consequences? What are the current interventions?

## Location of Brain Iron Deposits in DCI

As an important part of CNS, hippocampus has the function of learning and memory formation.<sup>22</sup> Diabetic models exhibited marked hippocampal atrophy and impaired synaptogenesis leading to memory deficits.<sup>23,24</sup> Recent studies have confirmed that there is obvious iron deposition in the hippocampus of type 1 diabetes mellitus (T1DM) model, through an iron assay kit.<sup>25</sup> Similarly, type 2 diabetes mellitus (T2DM) has demonstrated increased iron content throughout the hippocampus, including cornu ammonis (CA) 1 region, CA3 region, and the dentate gyrus (DG) region,<sup>19,26</sup> while neurons in the hippocampal DG–CA3–CA1 circuit form neural representations of space and support spatial navigation and episodic memory.<sup>27</sup> Noteworthy, increased iron uptake in hippocampal neurons in T2DM triggers cell death, and damage to multiple regions of the hippocampus may be involved.<sup>28</sup> Similar to neurons, hippocampal astrocytes in T2DM models have been found to exhibit iron hyperuptake and to be associated with astrocyte polarization.<sup>29</sup> This is an important finding, as iron transfer from the periphery into neurons is tightly regulated by astrocytes.<sup>30</sup> Additional evidence suggests that iron supplementation increases the activation of microglia in the hippocampus of T2DM rats, which also leads to exacerbation of existing neuroinflammation and exacerbates the risk of neurodegenerative diseases.<sup>31</sup> In short, iron overload occurs in both neurons and glia (astrocytes and microglia) as an exacerbating factor in DM-induced hippocampal damage. This extensive iron deposition may be a notable factor triggering memory cognitive dysfunction.

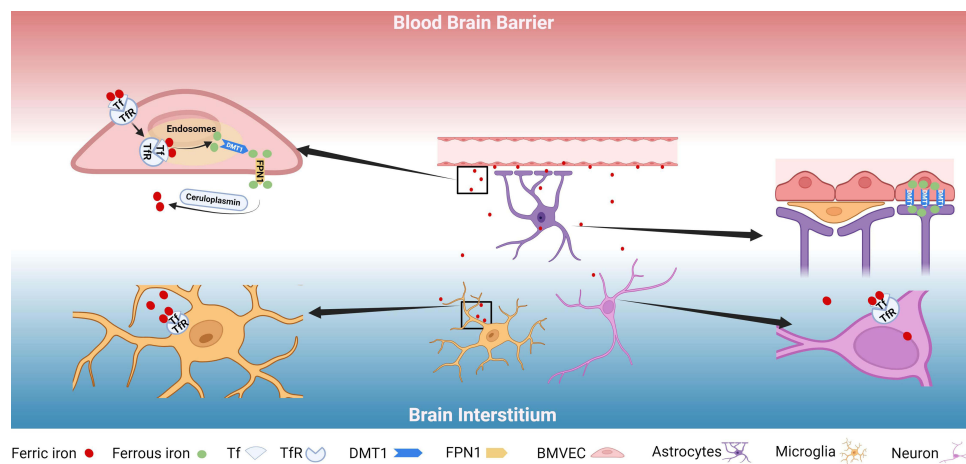
The basal ganglia, including the striatum (putamen, caudate, and pallidum), the substantia nigra, and the subthalamic nucleus, are responsible for executive function, working memory tasks, adaptive motor, and sensorimotor learning.<sup>32</sup> Using quantitative sensitivity mapping (QSM), T2DM patients with mild cognitive impairment were found to have greater iron deposition in the right caudate nucleus, substantia nigra, and left putamen, which are strongly associated with cognitive impairment.<sup>33</sup> In addition, excessive iron deposition in the putamen of T2DM patients was further confirmed,<sup>34</sup> which may affect cortico-striato-thalamocortical neural pathways and impede normal neurotransmission, manifesting as dysfunction of voluntary movement, cognition, language, and sensory.<sup>34</sup> Similarly, iron deposition in the striatum and frontal lobe of T2DM patients was elevated as assessed by quantitative imaging QSM and may contribute to the decline in executive function in T2DM.<sup>35</sup> Iron in the hypothalamus of T1DM rats is excess and imbalanced, showing increased cytoplasmic iron stores and decreased mitochondrial iron stores. This dysregulation can lead to neuronal degeneration and imbalances in energy homeostasis.<sup>36</sup> The above studies confirmed the iron deposition in the basal ganglia and tightly connected areas (cortex and thalamus) induced by DM, and the abnormalities in multiple cognitive functions caused by this should also be taken seriously.

It has been confirmed that in the T2DM mouse model cerebellum contains higher levels of monoamine oxidase (MAO)-A and -B, an enzyme that catalyzes the oxidative deamination of biogenic amines, which promotes the loss of neurotransmitters such as dopamine and 5-hydroxytryptamine. live.<sup>37</sup> The multifunctional iron-chelating drug M30 inhibited the enhanced MAO-A activity and decreased the MAO-B activity.<sup>37</sup> Although the literature is limited, this may indirectly reflect the importance of iron homeostasis in the cerebellum of diabetic models on dopaminergic metabolism, which deserves further exploration and confirmation.

## Mechanisms of Brain Iron Deposition in DCI

### Cellular Iron Metabolism and Regulation in the Brain

Brain iron uptake first crosses the blood-brain barrier (BBB)- composed mainly of brain microvascular endothelial cells (BMVEC) and astrocytes.<sup>38</sup> Specifically, ferric transferrin (Tf) enters BMVEC by binding to the transferrin receptor (TfR), and forms endosomes. Due to the change of microenvironment pH, Fe dissociates from Tf and reduces from ferric ion to ferrous ion, and then releases the reduced iron into the cytoplasm through divalent metal-ion transporter-1 (DMT1). Finally, it leaves BMVEC through ferroportin (FPN) and is exported into the brain interstitial fluid, accompanied by the oxidation of ferrous ions by ceruloplasmin (mostly synthesized and released by the choroid plexus) to iron ions and loaded onto Tf<sup>38,39</sup> (Figure 1).



**Figure 1** Iron enters the brain and is transported to neurons and glial cells. Iron-binding Tf binds to TfR and is internalized in endosomes. Acidification of endosomes dissociates Fe from Tf and reduces it to ferrous ions, which are subsequently released into the cytoplasm by DMT1. Finally, ferrous ions leave BMVECs through FPN1 and are exported into the interstitial fluid of the brain, where they are oxidized to ferric by ceruloplasmin. Neurons and microglia mainly take up Fe through the Tf-TfR system, while astrocytes can take up iron directly from BMVECs through DMT1. Created with Biorender.com.

After crossing the BBB, ferric transferrin in the interstitial fluid is taken up by neurons and glial cells through TfR-mediated endocytosis to meet their metabolic needs,<sup>40</sup> and neurons absorb ferric iron.<sup>41</sup> In addition, DMT1 is strongly expressed in the peduncles of astrocytes that directly contact BMVEC, suggesting the ability to uptake amounts of non-Tf-bound iron directly from the BBB.<sup>42–44</sup> Although it is speculated that neuronal DMT1 has the role of non-transferrin binding uptake, this has not been fully confirmed *in vivo*.<sup>45</sup> As the only known iron exporter, FPN1 widely exists in BMVEC, neurons and various glial cells, which dominates the release of iron in nerve cells in the brain<sup>46</sup> (Figure 1). Thus, CNS iron uptake is tightly regulated, and iron homeostasis in any neural cell requires a balance of uptake and export.

## Iron Overload Mechanism of DCI

As mentioned before, the iron absorption process begins at the BBB. Although increased iron exposure may lead to iron accumulation in multiple areas, the BBB may be the first area of the brain attacked by excess iron. The study found that the integrity of the BBB permeability in the cortex and striatum of DM rats was damaged after stroke. While the application of the iron chelator effectively protected the BBB, conversely confirming the contribution of iron overload in the destruction of the BBB induced by DM.<sup>47</sup> In addition, iron promoted the death of primary BMVEC isolated from DM animals, while iron chelator could effectively increase the viability of BMVEC.<sup>47</sup> Recent reports indicate that iron chelator can protect the integrity of glial vessels and improve the survival of endothelial cells in the brain of female DM mice.<sup>48</sup> Although the protection of the BBB is unquestionable, the targets and regulatory mechanisms of iron chelator in both sexes seem to be inconsistent, prompting researchers to pay attention to the differences in sensitivity to iron accumulation caused by different sexes and the impact on the BBB.

Cellular iron homeostasis is carefully regulated by multiple proteins, including TfR1 as an iron uptake protein and FPN1 as an export protein.<sup>49</sup> The study found that TfR1 was upregulated and FPN1 was downregulated in hippocampus of T2DM model, which may be an important factor causing neuronal iron overload. Similarly, downregulation of the FPN1 gene expression in the hippocampus was also found in T1DM rats.<sup>19,25</sup> A recent report showed increased co-expression of DMT1 with reactive astrocytes in the hippocampus of T2DM mice.<sup>29</sup> Considering that upregulation of DMT1 expression leads to iron accumulation, which further promotes astrocyte activation,<sup>50</sup> this may partly explain the structural and metabolic abnormalities of astrocytes induced by DM.<sup>51,52</sup> This seems to be a good understanding of why iron overload occurs. Simply put, more iron enters the cells and less exits.

Changes in ferritin expression should also be of concern. Ferritin is a hollow iron storage protein, consisting of a heavy chain (FTH) and a light chain (FTL), which can store a large amount of free iron entering cells until the cavity is

saturated, thus protecting cells from iron toxicity damage.<sup>53,54</sup> In general, the composition of ferritin varies greatly in different cells. Most of the ferritin in tissues with iron storage function is FTL, which has a more stable structure and stores more iron; while tissues with high iron oxidation activity mainly contain FTH, which has significant antioxidant activity.<sup>55,56</sup> In the brain, neurons mainly express FTH, while glial cells mainly express FTL.<sup>57–59</sup> It has been confirmed that FTH expression is significantly decreased in the hippocampus of T2DM model,<sup>19</sup> which may represent the presence of a large amount of free iron in cells. This severely affects neuronal survival as free iron (especially ferrous iron) is a key factor in promoting cellular oxidative damage and lipid peroxidation,<sup>60</sup> and low expression of FTH is insufficient to counteract them. In fact, iron buffer and ferritin are mainly found in glial cells rather than neurons.<sup>61</sup> FTL did not show significant differential expression in T2DM brains,<sup>19,29</sup> which may represent a saturated state of iron stores and an inability to accommodate excess iron. Interestingly, the level of ferritin was significantly increased in the hippocampus of T1DM rats, without distinguishing between FTL and TFH.<sup>62</sup> This seems to indicate differential regulation of ferritin in different types of DM brains, which requires further investigation of the specific mechanisms.

In addition to the classical mechanisms of iron regulation, it is also important to focus on specific proteins or channels that regulate iron metabolism. The study found upregulation of lipocalin-2 (LCN2) in the hippocampus and lipopoly-saccharide/high glucose-treated neurons of DM mice, which may promote DCI.<sup>63</sup> Although the researchers did not mention the significance of DM-induced LCN2 elevation on iron overload, it was confirmed that the expression of LCN2 in the brain was positively correlated with iron overload in various brain regions.<sup>64</sup> In fact, LCN2 is a transferrin-independent iron transporter that associates with siderophore and participates in cellular iron transport.<sup>65</sup> It has also been reported that L-type calcium channels are the main way for cells to take up ferrous iron when iron content increases.<sup>66</sup> Whether LCN2 and L-type calcium channels are involved in DM-induced brain iron deposition remains to be further confirmed.

## Factors of Diabetic Brain Iron Deposition

As mentioned above, complex regulation of iron-related proteins maintains cellular iron acquisition, utilization and elimination, but they are often intervened differently. It has been confirmed that hepcidin is the main factor regulating iron metabolism.<sup>67</sup> As an antimicrobial peptide, hepcidin is mainly secreted in the liver,<sup>67</sup> also expressed in the brain.<sup>68</sup> It has been reported that hepcidin deficiency in T2DM may result in iron deposition in the hippocampus and consequent cognitive impairment.<sup>69</sup> The researchers did not explore the specific consequences of underexpression of hepcidin, but hepcidin has been shown to regulate the expression of iron transporters such as TfR1, DMT1, and FPN1 in BMVEC.<sup>70</sup> Interestingly, many studies have demonstrated the downregulation of FPN1 in the DM hippocampus,<sup>19,25,29</sup> which seems to contradict the conclusion of low expression of hepcidin, because hepcidin binds to FPN1 and functionally down-regulates FPN1 to affect iron availability.<sup>71</sup> In addition, the expression rate of hepcidin in the brain is low and a considerable part actually comes from the liver,<sup>68</sup> but the expression of hepcidin in DM patients has a completely opposite conclusion.<sup>72,73</sup> This may be due to the characteristics of different diabetic patients and the complex regulatory factors of hepcidin, but may the same be true of hepcidin levels in the brain?<sup>62</sup> More experimental and clinical studies are needed to confirm or refute the specific role of hepcidin in DM.

In any case, the contribution of hyperglycemia should not be ignored, as it is the most important pathological outcome of DM. Neurons have a continuously high demand for glucose, and neuronal uptake of glucose depends on the concentration of extracellular glucose. Therefore, persistent hyperglycemia induced by DM can lead to a multiplied increase in neuronal glucose levels, and excessive glucose metabolism can lead to neuronal damage, known as glucose neurotoxicity.<sup>74</sup> Studies have found that diabetic hyperglycemia aggravates neuronal death by inhibiting the transcription and secretion of lactoferrin in neutrophils and accumulating iron in neurons.<sup>75</sup> In addition, earlier reports suggested a positive correlation between serum ferritin and serum glucose levels.<sup>76</sup> In the periphery, excess iron interferes with glucose metabolism and causes DM by disrupting insulin signaling,<sup>77,78</sup> whereas iron reduction has been shown to improve pathological hyperglycemia.<sup>79,80</sup> Thus, a high-glucose environment promotes iron overload and vice versa. However, due to the lack of reports, the specific mechanisms leading to hyperglycemia and iron metabolism disorders still need to be further explored.

As the main pathological factor of T2DM, insulin resistance (IR) should also be mentioned. In fact, compared with T1DM, T2DM has a higher incidence of cognitive impairment, and T2DM induces neurological damage and cognitive impairment earlier than T1DM,<sup>81</sup> so more attention should be paid to the independent role of IR. IR triggers neuronal insulin signaling dysregulation, which may cause DCI.<sup>82–84</sup> Insulin resistance has been shown to induce redistribution of TfR on the cell surface, promoting iron overload.<sup>85,86</sup> In turn, iron overload and elevated ferritin levels inhibit insulin synthesis and secretion and induce IR.<sup>87,88</sup> It has been reported that abnormal iron metabolism aggravates memory impairment and neuronal survival in DM, mainly by exacerbating IR in the CNS.<sup>89</sup> Also be concerned about the crosstalk between IR and hepcidin: IR may have interfered with hepcidin expression and secretion, whereas treatment with hepcidin gene silencing improved IR.<sup>90,91</sup> Anyway, the role of IR on brain iron overload and the specific mechanism deserve further investigation.

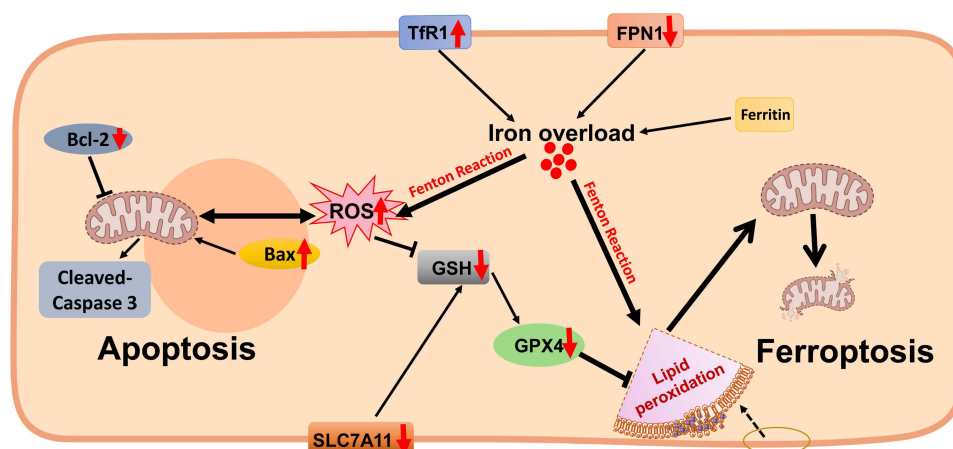
Attention should be paid to the promoting effect of inflammation on brain iron deposition in DM, as DM has been proved to be systemic chronic inflammation.<sup>92</sup> A number of inflammatory factors were confirmed to be significantly increased in DM model brains, such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)- $\alpha$ .<sup>93–95</sup> Note that these cytokines can enhance the strength of iron transport. It has been demonstrated that inflammation (especially the secretion of TNF- $\alpha$  and IL-6) increases iron accumulation in neurons due to the resulting upregulation of DMT1.<sup>96</sup> More studies have confirmed the consistency of DMT1 and TNF- $\alpha$  overexpression in CNS inflammation models.<sup>50,97</sup> Another interesting conclusion was the significant downregulation of FPN protein levels in neurons following inflammatory stimulation of TNF- $\alpha$  and IL-6, regardless of the effect of hepcidin.<sup>96</sup> In addition, increased DMT1 and TfR1 levels and decreased FPN1 were also observed in IL-1 $\beta$  or TNF- $\alpha$ -treated neurons.<sup>98</sup> In T1DM, iron deposition in the brain is mainly caused by inflammation-induced BBB and damage,<sup>99</sup> and neuronal iron deposition is also strongly associated with inflammation.<sup>62</sup> In fact, inflammation and iron overload are like a chicken-and-egg relationship. In other words, neuroinflammation in DM does not necessarily occur earlier than brain iron overload, because it has been reported that deferoxamine can target neuroinflammation to alleviate DCI.<sup>100</sup>

## Consequences of Brain Iron Deposition in DCI

As a factor that triggers or exacerbates DCI, brain iron accumulation has been confirmed to occur in multiple regions of the brain and act on a variety of cell damage. Considering the brain's high iron requirement and sensitivity to reactive oxygen species (ROS), brain iron accumulation and concomitant oxidative damage were confirmed to be associated with early DCI.<sup>101,102</sup> The biological function of iron is based on its redox ability, that is, the interconversion between the ferrous and ferric states.<sup>103</sup> At the same time, excess iron can be toxic due to iron's ability to exist in various oxidation states. Specifically, when an excess of iron is present, the formation of highly reactive hydroxyl radicals, an excess of hydrogen peroxide, and a deficiency of antioxidants can be catalyzed by the Fenton reaction<sup>104</sup> (Figure 2). A large number of studies have confirmed the increase of ROS in the brain of DM models, which is often accompanied by the weakening of antioxidant systems, such as superoxide dismutase (SOD), glutathione/glutathione disulfide (GSH/GSSG) and catalase (CAT).<sup>105–108</sup> It also showed elevation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) 2 and NOX4, the main endogenous biological systems for ROS formation.<sup>29</sup> It has been demonstrated that direct glucotoxicity in neurons is mainly due to increased intracellular glucose oxidation, leading to enhanced ROS production.<sup>109</sup> High glucose can also consume NADPH through the sorbitol pathway to disrupt the GSH cycle, reduce the ability of glutathione peroxidase to metabolize H<sub>2</sub>O<sub>2</sub> into water, and then increase the channel for H<sub>2</sub>O<sub>2</sub> to enter the Fenton reaction, thereby generating super hydroxyl radicals.<sup>74</sup> This oxidative stress may be the initiator of multiple pathological effects and interact through different pathways, eventually inducing the progression of brain damage in DM.<sup>110</sup>

Among the many targets of oxidative stress, lipids are the most implicated class of biomarkers. A large number of oxidants attack cell membranes, lipoproteins, and other lipid-containing structures, and lipid peroxidation occurs. Since the brain is rich in polyunsaturated fatty acids and relatively deficient in the oxidation system, lipid peroxidation easily occurs when the redox imbalance in the brain occurs.<sup>111</sup> As mentioned earlier, high levels of lipid peroxidation are an important cause of ferroptosis, so it is necessary to pay attention to changes in lipid peroxidation. Malondialdehyde is a common lipid peroxidation product, while 4-hydroxynonenal, the most biologically active lipid peroxidation product,





**Figure 2** Excess iron-induced cell death in the diabetic brain. The expression of Tfr1 and DMT1 is up-regulated in the diabetic brain (especially in hippocampal neurons), and the expression of FPN1 is down-regulated, which may lead to iron overload. As a direct consequence, iron overload can increase ROS and lipid oxide levels and reduce antioxidant activity such as GSH through the Fenton reaction. On the one hand, this leads to the damage of mitochondrial structure and function, the down-regulation of GPX4 and SLC7A11 protein expression and triggers neuronal ferroptosis; on the other hand, it may lead to the up-regulation of Bax protein and the down-regulation of Bcl-2 protein, triggering apoptosis. Some of the materials in Figure 2 are created with Biorender.com.

has various cytotoxic effects of lipid peroxidation, such as depletion of GSH, dysfunction of structural proteins, reduction of enzyme activity, and induction of cell death,<sup>112</sup> which have been shown to affect the severity of diabetic complications.<sup>19,29,105–108</sup> Note that iron is also an important component of lipid peroxidase subunits. High glucose and palmitic acid treatment increased  $\text{Fe}^{2+}$  in mouse hippocampal primary neurons, which in turn increased ROS and lipid peroxidation levels and decreased GSH concentration and GSH/GSSG ratio.<sup>26</sup> Similarly, under high glucose concentration environment, iron overload can aggravate the oxidative stress injury of PC12 neurons, possibly through the NF-E2-related factor 2 (Nrf2) /ARE signaling pathway.<sup>113</sup> Interestingly, administration of deferoxamine did effectively reverse excessive protein carbonylation in the prefrontal cortex and hippocampus of the DM model, but had no effect on the activity of antioxidant enzymes.<sup>108</sup> This is understandable since oxidative stress does not occur solely due to iron overload, as confirmed by other reports.<sup>114,115</sup>

Ferroptosis has been shown to be involved in the development of various diabetic complications,<sup>116,117</sup> also with neurodegeneration.<sup>89</sup> Ferroptosis, first proposed in 2012, is a regulated non-apoptotic form of cell death mainly due to inactivation of glutathione peroxidase 4 (GPX4) and iron-dependent lipid peroxidation.<sup>118,119</sup> Excess iron accumulates in cells and generates a large number of ROS, which provide a powerful oxidant for lipid peroxidation and lead to the biogenesis of polyunsaturated fatty acids and the occurrence of ferroptosis.<sup>120,121</sup> Iron overload is a key factor of ferroptosis, and the use of iron chelators can effectively reduce the occurrence of ferroptosis in various experimental models.<sup>118,122</sup> The presence of ferroptosis in DCI has been widely documented. Downregulation of GPX4 and solute carrier family 7 member 11 (SLC7A11) in the hippocampus of T2DM models triggered ferroptosis, manifested by abnormalities in mitochondrial membranes and collapse of mitochondrial cristae,<sup>19,26,28,123</sup> especially in neurons<sup>26,28</sup> (Figure 2). Similarly, T1DM has also been focused on the presence of ferroptosis in the hippocampus, including damage to neuronal mitochondria.<sup>25</sup> It has also been reported that epidermal growth factor/Nrf2/heme oxygenase-1 signaling and the microbiota-gut-brain axis regulate ferroptosis in T2DM hippocampal neurons.<sup>124</sup> Ferroptosis of BMVECs in T2DM should also be taken seriously, as this may exacerbate BBB disruption and cognitive impairment after diabetic stroke,<sup>47</sup> possibly related to the p53/GPX4 axis.<sup>125</sup> Overall, iron overload plays an important role as well as ferroptosis, especially in the context of DM-induced cognitive decline,<sup>89</sup> and onset of iron overload may be the main driver of ferroptosis.

Apoptosis, also known as programmed cell death, occurs during normal physiological processes (development and aging) and acts as a homeostatic mechanism to maintain cell populations.<sup>126</sup> Inappropriate apoptosis can induce a variety of diseases, including neurodegenerative diseases, ischemic injury, autoimmune diseases and many types of cancer. A number of evidences have shown that hyperglycemia and its metabolic disorders can cause necrosis and apoptosis of nerve cells, and there is a significant correlation with DCI.<sup>127–129</sup> Iron damages membrane lipids, proteins, and nucleic

acids through ROS toxicity, thereby increasing neuronal apoptosis and affecting its function.<sup>130</sup> A new pathway for the induction of apoptosis under glucolipotoxic conditions has been identified, involving increased iron import, triggered by depletion of mitochondrial membrane potential and generation of hydroxyl radicals from hydrogen peroxide by the Fenton reaction.<sup>131</sup> Susceptibility to apoptosis has been shown to be controlled by the proapoptotic B-cell lymphoma-2 (BCL2) homologue family. Briefly, upregulation of pro-apoptotic Bcl-2-associated X protein (Bax) and downregulation of the homologous anti-apoptotic Bcl-2 protein, as well as activated cleavage of Caspase-3, are important mechanisms of apoptosis.<sup>126</sup> Up-regulated Bax and down-regulated Bcl-2 in the hippocampus of iron-overloaded rats confirmed the role of iron accumulation in promoting neuronal apoptosis<sup>132</sup> (Figure 2). Although no direct evidence was found to confirm the role of iron overload in DM brain on apoptosis, follow-up studies should be considered.

## Treatment Strategies for DCI and Brain Iron Deposition

It is well known that good glycemic control significantly reduces the risk of DM complications and improves diabetic complications. However, studies have found that simple control of blood glucose does not completely prevent the occurrence and progression of complications, especially CNS lesions.<sup>133,134</sup> In other words, blood glucose levels had a limited effect on DCI.<sup>133,134</sup> Therefore, it makes sense to test antidiabetic drugs to treat cognitive impairment or to focus on other drugs that improve DCI.

Liraglutide, a glucagon-like peptide-1 receptor agonist, is clinically approved for obesity and T2DM.<sup>135</sup> The protective effects of liraglutide against neurodegeneration and cerebral ischemic events have been extensively demonstrated,<sup>136</sup> also involving DCI,<sup>137,138</sup> beyond its hypoglycemic effect. Our previous studies demonstrated the broad effects of liraglutide on hippocampal iron overload in T2DM models, including neurons and astrocytes, which in turn improved DCI.<sup>19,29</sup> In fact, liraglutide also had a significant effect on iron deposition in the DM liver, which is the first major metabolic organ of iron.<sup>139</sup> These findings seem to encourage the use of liraglutide against DCI and brain iron overload, but further confirmation by clinical trials is needed.

As mentioned earlier, numerous studies have confirmed the contribution of iron overload to DCI, which makes it possible to intervene by means of iron chelation. Studies have confirmed the favorable effects of deferoxamine in alleviating DCI by inhibiting oxidative stress, neuroinflammation and regulating iron homeostasis.<sup>100</sup> In addition, the application of deferoxamine can regulate the immune content of c-Jun N-terminal kinase, mitogen-activated protein kinase-38, brain-derived neurotrophic factor, and protein kinases A and C in the prefrontal cortex, hippocampus, amygdala, and nucleus accumbens of DM rats, confirming its regulatory effect on intracellular pathways in brain regions.<sup>140</sup> In a post-stroke memory impairment model in DM, deferoxamine prevented DM-mediated glial vascular remodeling and compromised BBB integrity, while improving diabetic memory function, suggesting a new therapeutic strategy for iron chelation to maintain glial vessel integrity and improve endothelial cell survival.<sup>48</sup> Similarly, deferoxamine treatment prevented vascular regression and microglial activation in DM rats and improved aquaporin-4 polarity and BBB permeability, while reducing iron overload-induced BMVEC ferroptosis and lipid peroxidation, and improving post-stroke cognitive impairment in DM.<sup>47</sup> Although iron chelation has been recognized as a means of improving various diabetic complications,<sup>141,142</sup> it should be used with caution in clinical practice, because iron deficiency caused by inappropriate iron chelation is also harmful.

Traditional Chinese medicine (TCM) seems to have received some attention and recognition in the prevention and treatment of DCI. TCM is characterized by multi-component, multi-target interactions with few adverse reactions.<sup>143</sup> In addition to compounds, the main active ingredient of a certain drug may also prove to have a protective effect against DCI. Danggui-Shaoyao-San has been shown to balance oxidant/antioxidant levels, improve the expression of neurotrophic factors and reduce neuronal apoptosis, thereby alleviating DM-induced cognitive dysfunction.<sup>144</sup> Furthermore, in addition to anti-neuron injury, Danggui-Shaoyao-San also has a good effect on physiological regulation such as iron metabolism.<sup>145</sup> Berberine, the main component of *Coptis chinensis* Franch., has been shown to play a protective role against DCI by reducing hippocampal neuron damage, improving tau protein hyperphosphorylation and repairing axonal damage.<sup>146,147</sup> Interestingly, berberine treatment can reduce cellular iron overload through proteins that regulate iron uptake.<sup>148</sup> Although TCMs may have multiple effects including improving DCI and regulating iron metabolism, valid pharmacological and toxicological evaluations are required.

Lifestyle changes and the need for ongoing self-regulation are major components of DM care. Studies have found that DM and its complications can be largely prevented and alleviated through interventions that promote lifestyle changes, such as a healthy diet and regular physical exercise.<sup>149</sup> Although lifestyle interventions do not appear to significantly change the prevalence of DCI,<sup>150,151</sup> the beneficial effects of various lifestyle interventions on neurodegeneration have been demonstrated,<sup>152</sup> so more specific forms of lifestyle intervention may Targeted and beneficial changes to DCI.<sup>153</sup> Note that in animal models, low-iron diets significantly improved DM (mainly showing significant increases in insulin sensitivity and beta-cell function).<sup>78</sup> Could this benefit apply to DCI? More clinical and experimental evidence is still needed.

## Conclusions

Due to the link between iron overload and DCI, the “iron” factor of brain injury in DM has been emphasized. Here, we review the distribution, mechanisms, causes, and consequences of iron overload in the DM brain, and try to discover drugs that can effectively intervene. In fact, the specific mechanism of the relationship between iron metabolism and DCI is not fully understood, and the pathological consequences of iron overload also need to be further explored. Based on the above reports, we believe that controlling iron metabolism in the central nervous system may be a promising therapeutic approach for DCI, but the vast majority of reports still use basic research, and these still need to be translated into evidence for clinical trials.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This research was supported by the General project of Education Department of Liaoning Province (No: L202027); Applied Basic Research Program of Liaoning Province (No: 2022JH2/101300108, 2023JH2/101300050); Project of Liaoning Provincial Department of Education (No: LJKMZ20221980).

## Disclosure

The authors declare no conflicts of interest in this work.

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