ISSN: 2754-4737

Journal of Neurology Research Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Research Progress on Relationship between Iron Metabolism and Type 2 Diabetes and Intervention Effect of GLP-1

Ren Jie, Liu Rui and Qin Jie*

Fifth Clinical Medical College of Shanxi Medical University, Shanxi, China

ABSTRACT

Iron metabolism plays a regulatory role in a variety of metabolic diseases, and certain levels of serum iron are essential for maintaining homeostasis in the body, while excessive iron accumulation increases the risk of metabolic diseases, especially type 2 diabetes mellitus (T2DM). Pathological processes such as iron deposition, iron ptosis and iron death can activate oxidative stress, lipid peroxidation, autophagy, etc., promote the amplification of the inflammatory cascade in the body, reduce antioxidant capacity, resulting in the gradual decline of islet β cell function, thereby promoting the occurrence and development of DM. Similarly, iron metabolism regulation plays an important role in complications such as diabetic target organs. Glucagon-like peptide-1 (GLP-1) is an important physiological sex hormone secreted by intestinal L cells. GLP-1 analogues or GLP-1 receptor agonists can regulate the process of iron metabolism, reduce iron overload or iron death-related inflammatory response, promote islet β cell proliferation and differentiation, and then improve insulin resistance and inhibit endothelial cell injury, playing an important role in the prevention and treatment of T2DM and its complications.

***Corresponding author**

Qin Jie, Fifth Clinical Medical College of Shanxi Medical University (Shanxi 030012), Tel: 13835121009; China.

Received: July 18, 2023; **Accepted:** July 26, 2023; **Published:** August 25, 2023

Keyword: Iron Metabolism, Pancreatic β-cell, Diabetes, GLP-1

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by glucose and lipid metabolism disorders, which are mainly characterized by decreased number, hypofunction and increased apoptosis of pancreatic β-cells. It has been shown that the mechanisms involved in the development of T2DM caused by multidimensional pathogenic responses in pancreatic β-cells include pathological processes such as cell iron death, endoplasmic reticulum (ER) stress, reactive oxygen species activation, membrane disruption, and receptor-mediated signaling impairment transduction cascades [1]. Iron metabolism plays an important role in the development and progression of a variety of metabolic diseases, especially T2DM.The first case to investigate the relationship between iron metabolism and diabetes is hereditary hemochromatosis (HH), and the specific mechanism of HH-associated diabetes pathogenesis remains incompletely clarified, and insulin deficiency and insulin resistance (IR) may be important contributing factors. Patients with HH are unable to regulate insulin secretion levels in a timely manner due to the decline of pancreatic β-cell function, so the risk of developing diabetes is significantly increased when IR is present [2, 3]. Experiments have shown that iron accumulation is an important determinant of islet cell inflammation and has been considered as a biomarker of the risk of diabetes development and mortality [4]. When iron homeostasis is impaired in vivo, it can lead to iron overload and increased reactive oxygen species, thus affecting insulin synthesis and secretion, affecting the regulation of glucose homeostasis in vivo, and dietary iron restriction can improve islet β cell function and glucose tolerance in obese mice [5]. At the same time, excessive iron accumulation triggers oxidative stress and transforms into a macrophage pro-inflammatory state, which has some correlation with steatosis and late complications of diabetes in T2DM, such as diabetic cardiomyopathy, retinopathy, nephropathy, and neuropathy, and can significantly affect the mortality of diabetes and its related complications [6, 7]. Studies have confirmed that there is also a certain correlation between iron metabolism and the level of adiponectin (ADPN), which can improve placental damage caused by gestational diabetes by correcting iron death induced by fatty acid oxidation/peroxide imbalance [8].

Iron dysfunction is associated with T2DM, particularly iron deposition in islet cells. Animal studies have shown that iron concentrations in both serum and pancreatic tissue are increased in T2DM mice, with massive ferritin deposition around pancreatic β-cells, suggesting a large iron overload in pancreatic tissue, indicating that iron overload is involved in the progression of T2DM. Excess tissue iron may help explain the loss of β-cells in T2DM, as cellular iron import is upregulated by iron import protein (DMT1), which confers iron toxicity to pancreatic β-cells [9, 10]. Iron metabolism disorders also lead to mitochondrial defects, which are important for β-cell damage in the progression of T2DM. However, the presence of ferrin levels in T2DM patients is a marker of increased iron storage in the body, indicating that diabetes may also be involved in regulatory mechanisms of iron homeostasis. Although there are now numerous studies confirming that iron overload is associated with the risk of diabetes, iron deficiency is associated with obesity, another major risk factor for diabetes, and the combination of obesity and iron overload particularly easily leads to the development of T2DM through the combination of insulin deficiency and insulin resistance [11].

Iron ptosis is cell death induced by iron dysregulation characterized by intracellular lipid peroxidation and iron accumulation, which is different from apoptosis and necrosis, and has been reported to be closely related to a variety of diseases, such as metabolism-related diseases, tumors, and immune diseases [12]. Because pancreatic β-cells express low levels of antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase, they lack strong antioxidant capacity and easily lead to the accumulation of reactive oxygen species, which easily triggers the occurrence of iron ptosis.In mouse MIN6 cells, iron ptosis and insulin secretion dysfunction have been found to be induced when the endoplasmic reticulum stress-related pathway (PERK pathway) is activated [13]. High glucose (HG), hydrogen peroxide (H2O2), or streptozotocin (STZ) can all act as inducers of iron ptosis, promote pancreatic β-cell apoptosis, and significantly decrease insulin secretion (GSIS) levels from glucose, while treatment with ferrostatin-1 (Fer-1) or deferoxamine (DFO), an inhibitor of iron ptosis, can reduce the damage to GSIS and has a certain protective effect on pancreatic β-cells [14, 15]. Zhou et al found that iron ptosis is closely related to IR, and cryptochlorogenic acid (CCA), an extract of mulberry leaves, can achieve antioxidant and protective effects on diabetes by increasing glutathione peroxidase 4 (GPX4) levels and activating the Xc-/GPX4 system as well as Nrf2, thereby inhibiting iron ptosis and improving diabetes-induced lipid peroxidation and oxidative stress processes [16, 17]. Meanwhile, to a certain extent, CCA can promote islet cell regeneration, reduce islet cell damage caused by hyperglycemia, and promote islet β-cell regeneration [14]. Many animal and clinical studies have also confirmed the presence of varying degrees of iron deposition in various tissues of diabetes, which may be a further cause of iron ptosis [18, 19]. Iron ptosis is involved in GSIS injury and arsenic-induced islet cell injury, which plays an important role in maintaining homeostasis and glucose metabolism homeostasis in islet cells [20]. Therefore, monitoring and controlling factors associated with iron ptosis may be one of the new intervention targets for the early diagnosis and treatment of T2DM [21]. Similarly, studies have shown that iron ptosis and ferrite phagocytosis play an important role in the development and progression of diabetic complications such as diabetic nephropathy, diabetic cardiomyopathy, diabetic atherosclerosis, diabetic stroke and neurodegenerative changes, which may be related to the involvement of iron metabolism in diabetes-induced endothelial dysfunction, and inhibition of iron ptosis has a protective effect on ischemia-reperfusion injury in diabetic cardiomyocytes [12, 22-25]. The specific mechanism by which iron ptosis is involved in diabetes-induced endothelial dysfunction is not fully clarified, and reports have shown that p53 signaling is activated during the course of diabetes, further activating the p53-XCT (substrate-specific subunit of system XC-) -glutathione (GSH) axis, resulting in reduced glutathione synthesis, which is involved in triggering endothelial cell iron ptosis, thereby leading to impaired endothelial function [26]. While there are currently few studies on the role of iron death in diabetic liver injury, it is necessary to explore this aspect because it promotes various complications of fatty liver and T2DM [27].

Iron death is a specific form of regulated cell death that is accompanied by iron-dependent increases in lipid peroxides. Quercetin, as a natural iron chelator in the plant kingdom, is beneficial for a variety of iron overload-related diseases in the body. Li et al first demonstrated that quercetin can exert anti-inflammatory and antioxidant effects, reduce oxidative stress in pancreatic β-cells, and improve insulin resistance (IR) in peripheral tissues by inhibiting iron deposition in pancreatic and endothelial cells and iron death in pancreatic β-cells, which has become one of our new approaches to prevent and treat T2DM. In addition, quercetin may represent a potential therapeutic chemical involved in iron death during the development of T2DM [28, 29-32].

Second, the effect of GLP-1 on iron metabolism in T2DM and its complications

It has been shown that lipid peroxidation, antioxidant capacity reduction and mitochondrial morphological and structural changes in pancreatic β-cells are consistent with the pathological process of cellular iron death during the development of T2DM. Liraglutide (LIRA), as a GLP-1 analogue commonly used in clinical practice, has been demonstrated to have a good effect in improving pancreatic β-cell function and increasing β-cell mass [33, 34]. LIRA attenuated iron deposition by decreasing transferrin receptor (TFR1) expression and increasing iron export protein (FPN1) expression, and increased the expression of Nrf2/HO-1/GPX4 signaling pathway in the liver of diabetic mice to reduce iron death. In addition, LIRA reduces high glucose-induced high levels of labile iron pools (LIPs) and intracellular reactive oxygen species accumulation in vitro. Reports have proposed that LIRA ameliorates diabetes-induced liver fibrosis, which may be associated with inhibition of the iron death pathway [27]. Therefore, we hypothesize that LIRA plays a crucial role in reducing iron accumulation, oxidative damage, and iron death in diabetic mice. Meanwhile, LIRA could play a protective role in the presence of high glucose by inhibiting autophagy in HK-2 cells and kidney cells of diabetic rats. While another study proposed that LIRA attenuates glucolipotoxicity in pancreatic β-cells by activating autophagy [35]. These studies suggest that the mechanisms underlying autophagic dysfunction under different conditions may determine the effects of GLP-1 analogues.

An and other teams have demonstrated for the first time in T2DM models that iron death often occurs in the hippocampus, and LIRA can further inhibit iron death by increasing the expression of GPX4 and glutamate/cystine reverse transporter (SLC7A11) and inhibiting excessive acyl-CoA synthase long chain family member 4 (ACSL4) to reduce oxidative stress, lipid peroxidation, and iron overload in diabetic cognitive impairment, thereby attenuating damage to hippocampal neurons and synaptic plasticity and ultimately restoring cognitive function, which provides a new means for the prevention and treatment of diabetes-related cognitive dysfunction. Exenatide, as a novel GLP-1 receptor agonist, has recently been demonstrated to improve glucose homeostasis by increasing insulin release and inducing Frataxin and Fe-S cluster protein expression to reduce oxidative stress, further elucidating the relationship between iron homeostasis maintenance and functional reserve in pancreatic β-cells. At the same time, exenatide induced Frataxin and iron-sulfur cluster protein expression in pancreatic β-cells and sensory neurons, decreased oxidative stress and apoptosis, improved mitochondrial function, and protected sensory neurons in dorsal root ganglia [36, 37].In conclusion, more and more studies have confirmed that iron metabolism disorders are closely related to the occurrence and development of diabetes, low levels of iron in the body are closely related to obesity and can increase the risk of diabetes, while when iron overload in the body, it can promote the activation of oxidative stress response and the occurrence of inflammatory response in the body, especially the damage to pancreatic β-cells, which can lead to decreased insulin levels and promote the occurrence and development of diabetes. At present, there are few studies on the specific mechanism of iron metabolism on the development of diabetes and its chronic complications, and more evidence

may be needed to support iron metabolism as one of the new targets for intervening T2DM and its related complications in the future. In summary, appropriate serum iron levels play an important role in maintaining homeostasis, and drugs such as GLP-1 analogues and GLP-1 receptor agonists play an important role in increasing insulin sensitivity and enhancing anti-inflammatory and antioxidant capacity in diabetic patients, but their relevant studies on the process of cellular iron metabolism (such as iron deposition, iron death, etc.) still need to be further explored.

Fund project Natural Science Research Project of Shanxi Province (202203021211059); Graduate Education Innovation Project of Shanxi Province (2022Y394)

References

1. Chen X, Huang T, Shi Y, Luyin Wang Wei Li, et al. (2019) A GLP1 receptor agonist attenuates human islet amyloid polypeptideinduced autophagy and apoptosis in MIN6 cells. J Mol Med Rep 19: 1365-1371.
2. Buysschaert M, Paris I, Selvais P, Hermans MP (1997) Clinical aspects of diabetes secondary to idiopathic haemochromatosis in French-speaking Belgium. J Diabetes Metab 23: 308-313.
3. Simcox JA, McClain DA (2013) Iron and diabetes risk. J Cell Metab 17: 329-341.
4. Marku A, Galli A, Marciani P, Dule N, Perego C, et al. (2021) Iron Metabolism in Pancreatic Beta-Cell Function and Dysfunction. J Cells 10: 2841.
5. Vila CM, Marchi G, Barque A, Esteban-Jurado C, Marchetto A, et al. (2020) Genetic and Clinical Heterogeneity in Thirteen New Cases with Aceruloplasminemia. Atypical Anemia as a Clue for an Early Diagnosis. J Int J Mol Sci 21: 2374.
6. Altamura S, Mudder K, Schlotterer A, Fleming T, Heidenreich E, et al. (2021) Iron aggravates hepatic insulin resistance in the absence of inflammation in a novel db/db mouse model with iron overload. J Mol Metab 51: 101235.
7. Altamura S, Kopf S, Schmidt J, Müdder K, Rita da Silva A, et al. (2017) Uncoupled iron homeostasis in type 2 diabetes mellitus. J Mol Med (Berl) 95: 1387-1398.
8. Zheng Y, Hu Q, Wu J (2022) Adiponectin ameliorates placental injury in gestational diabetes mice by correcting fatty acid oxidation/peroxide imbalance-induced ferroptosis via restoration of CPT-1 activity. J Endocrine 75: 781-793.
9. Pinti MV, Fink GK, Hathaway QA, Durr AJ, Kunovac A, et al. (2019) Mitochondrial dysfunction in type 2 diabetes mellitus: an organ-based analysis. Am J Physiol Endocrinol Metab 316: E268-E285.
10. Hansen JB, Tonnesen MF, Madsen AN, Hagedorn PH, Friberg J, et al. (2012) Divalent metal transporter 1 regulates iron-mediated ROS and pancreatic beta cell fate in response to cytokines. Cell Metab 16: 449-461.
11. Alshwaiyat NM, Ahmad A, Wan HW, Hamid Ali Nagi Al-Jamal (2021) Association between obesity and iron deficiency (Review). Exp Ther Med 22: 1268.
12. Hu W, Liang K, Zhu H, Zhao C, Hu H, et al. (2022) Ferroptosis and Its Role in Chronic Diseases. Cells 11: 2040.
13. Zhang X, Jiang L, Chen H, Wei S, Yao K, et al. (2022) Resveratrol protected acrolein-induced ferroptosis and insulin secretion dysfunction via ER-stress- related PERK pathway in MIN6 cells. Toxicology 465: 153048.
14. Bruni A, Pepper AR, Pawlick RL, Gala-Lopez B, Gamble AF, et al. (2018) Ferroptosis-inducing agents compromise in vitro human islet viability and function. Cell Death Dis 9: 595.
15. Stancic A, Saksida T, Markelic M, Vucetic M, Grigorov I, et al. (2022) Ferroptosis as a Novel Determinant of beta-Cell Death in Diabetic Conditions. Oxid Med Cell Longev 2022: 3873420.
16. Jahng J, Alsaadi RM, Palanivel R, Song E, Barbosa Hipolito VE, et al. (2019) Iron overload inhibits late stage autophagic flux leading to insulin resistance. EMBO Rep 20: e47911.
17. Zhou Y (2020) The Protective Effects of Cryptochlorogenic Acid on beta-Cells Function in Diabetes in vivo and vitro via Inhibition of Ferroptosis. Diabetes Metab Syndr Obes 13: 1921-1931.
18. Eshak ES, Iso H, Maruyama K, Muraki I, Tamakoshi A (2018) Associations between dietary intakes of iron, copper and zinc with risk of type 2 diabetes mellitus: A large population-based prospective cohort study. Clin Nutr 37: 667-674.
19. Coffey R, Knutson MD (2017) The plasma membrane metal-ion transporter ZIP14 contributes to nontransferrin-bound iron uptake by human beta-cells. Am J Physiol Cell Physiol 312: C169-C175.
20. Wu X, Li Y, Zhang S, Zhou X (2021) Ferroptosis as a novel therapeutic target for cardiovascular disease. Theranostics 11: 3052-3059.
21. Sha W, Hu F, Xi Y, Chu Y, Bu S (2021) Mechanism of Ferroptosis and Its Role in Type 2 Diabetes Mellitus. J Diabetes Res 2021: 9999612.
22. Fang X, Cai Z, Wang H, Han D, Cheng Q, et al. (2020) Loss of Cardiac Ferritin H Facilitates Cardiomyopathy via Slc7a11-Mediated Ferroptosis. Circ Res 127: 486-501.
23. Weiland A, Wang Y, Wu W, Lan X, Han X, et al. (2019) Ferroptosis and Its Role in Diverse Brain Diseases. Mol Neurobiol 56: 4880-4893.
24. Bai T, Li M, Liu Y, Qiao Z, Wang Z (2020) Inhibition of ferroptosis alleviates atherosclerosis through attenuating lipid peroxidation and endothelial dysfunction in mouse aortic endothelial cell. Free Radic Biol Med 160: 92-102.
25. Latunde-Dada GO (2017) Ferroptosis: Role of lipid peroxidation, iron and ferritinophagy. Biochim Biophys Acta Gen Subj 1861: 1893-1900.
26. Luo EF, Li HX, Qin YH, Qiao Y, Yan GL, et al. (2021) Role of ferroptosis in the process of diabetes-induced endothelial dysfunctionJ. World J Diabetes 12: 124-137.
27. Song JX, An JR, Chen Q, Yang XY, Jia CL, et al. (2022) Liraglutide attenuates hepatic iron levels and ferroptosis in db/db mice. Bioengineered 13: 8334-8348.
28. Chen X, Li H, Wang Z, Zhou Q, Chen S, et al. (2020) Quercetin protects the vascular endothelium against iron overload damages via ROS/ADMA/DDAH/eNOS/NO pathwayJ. Eur J Pharmacol 868: 172885.
29. Eitah HE, Maklad YA, Abdelkader NF, Gamal El Din AA, Badawi MA, et al. (2019) Modulating impacts of quercetin/sitagliptin combination on streptozotocin-induced diabetes mellitus in rats. Toxicol Appl Pharmacol 365: 30-40.
30. Wang Z, Zhai D, Zhang D, Bai L, Yao R, et al. (2017) Quercetin Decreases Insulin Resistance in a Polycystic Ovary Syndrome Rat Model by Improving Inflammatory Microenvironment. Reprod Sci 24: 682-690.
31. Kose T, Vera-Aviles M, Sharp PA, Latunde-Dada GO (2019) Curcumin and (-)- Epigallocatechin-3-Gallate Protect Murine MIN6 Pancreatic Beta-Cells Against Iron Toxicity and Erastin-Induced Ferroptosis[J]. Pharmaceuticals (Basel) 12: 26.
32. Li D, Jiang C, Mei G, Zhao Y, Chen L, et al. (2020) Quercetin Alleviates Ferroptosis of Pancreatic beta Cells in Type 2 Diabetes. Nutrients 12: 2954.
33. Yaribeygi H, Sathyapalan T, Sahebkar A (2019) Molecular mechanisms by which GLP-1 RA and DPP-4i induce insulin

sensitivity. Life Sci 234: 116776.

34. Rodrigues T, Borges P, Mar L, Marques D, Albano M, et al. (2020) GLP-1 improves adipose tissue glyoxalase activity and capillarization improving insulin sensitivity in type 2 diabetes. Pharmacol Res 161: 105198.
35. Wang J, Wu J, Wu H, Xingzhen Liu, Yingjian Chen, et al. (2015) Liraglutide protects pancreatic beta-cells against free fatty acids in vitro and affects glucolipid metabolism in apolipoprotein E-/- mice by activating autophagy. Mol Med Rep 12: 4210-4218.
36. An JR, Su JN, Sun GY, Wang QF, Fan YD, et al. (2022) Liraglutide Alleviates Cognitive Deficit in db/db Mice: Involvement in Oxidative Stress, Iron Overload, and Ferroptosis. Neurochem Res 47: 279-294.
37. Igoillo-Esteve M, Oliveira AF, Cosentino C, Fantuzzi F, Demarez C, et al. (2020) Exenatide induces frataxin expression and improves mitochondrial function in Friedreich ataxia. JCI Insight 5: e134221.