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# Collaboration of Ferroptosis in Insulin Dependent Diabetes Persuade Adrenal Pathology

**Nevena Saksida***

*Department of Molecular Biology, Institute for Biological Research "Siniša Stanković", National Institute of Republic of Serbia, University of Belgrade, 11060 Belgrade, Serbia*

## Abstract

Cell death plays an important part in diabetes- convinced liver dysfunction. Ferroptosis is a recently defined regulated cell death caused by iron-dependent lipid peroxidation. Our former studies have shown that high glucose and streptozotocin( STZ) beget β cell death through ferroptosis and that ferrostatin- 1 (Fer- 1), an asset of ferroptosis, improves β cell viability, island morphology, and function. This study was aimed to examine *in vivo* the involvement of ferroptosis in diabetes- related pathological changes in the liver. For this purpose, manly C57BL/6 mice, in which diabetes was convinced with STZ (40 mg/kg/5 successive days), were treated with Fer- 1 (1 mg/kg, from day 1 – 21 day). It was set up that in diabetic mice Fer- 1 bettered serum situations of ALT and triglycerides and dropped liver fibrosis, hepatocytes size, and binucleation. This enhancement was due to the Fer-1-induced attenuation of ferroptotic events in the liver of diabetic mice, similar as accumulation of pro-oxidative parameters (iron, lipofuscin, 4-HNE), drop in expression position/ exertion of antioxidative defense- related motes (GPX4, Nrf2, xCT, GSH, GCL, HO-1, SOD), and HMGB1 translocation from nexus into cytosol. We concluded that ferroptosis contributes to diabetes- related pathological changes in the liver and that the targeting of ferroptosis represents a promising approach in the operation of diabetes- convinced liver injury.

**Keywords:** Ferroptosis • Liver • Diabetes • Oxidative stress • Lipid peroxidation • Nrf2

## Introduction

Diabetes mellitus is a habitual metabolic complaint that affects numerous organs including the liver. Diabetes- related pathological changes in the liver are reflected in the differences of biochemical serum parameters and morphological and ultrastructural variations in the organ itself. These differences in the liver start from adipose degeneration of liver cells and extend to steatohepatitis and periportal fibrosis. Likewise, diabetes is accompanied by profound differences in liver size which can be the result of changes in cell number, cell growth, and/ or cell death. Hepatocellular death is one of the most important contributing factors to diabetes- related liver pathology and progression of liver damage. thus, describing the types of cell death and its beginning mechanisms must be in the exploration concentrate with the final thing of targeted remedy for this serious diabetic complication [1].

Generally described types of hepatocellular death in diabetes are apoptosis, autophagy, and necrosis. Although biochemically and morphologically different, the underpinning mechanisms of all those types of cell death involve common factors disturbances in redox/antioxidant and seditious status. Both of these develop due to the diabetes- related hyperglycemia and hyperlipidemia and are tightly connected. We've lately shown that changes in oxidative state in diabetes induce redox revision of high- mobility group box 1 (HMGB1), an important motorist of inflammation signaling. These variations accordingly determine the type of cell death and the cross-talk between apoptosis and autophagy in the liver of diabetic creatures. We've also shown that melatonin exerts hepatoprotective goods against pronecrotic events in the liver in experimental diabetes due to its antioxidative parcels.

***Address for Correspondence:** Nevena Saksida, Department of Molecular Biology, Institute for Biological Research "Siniša Stanković", National Institute of Republic of Serbia, University of Belgrade, 11060 Belgrade, Serbia; E-mail: Nevenasaksida45@gmail.com*



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These data, along with plenitude of others, speak in favor of the benefit of antioxidants supplementation in the diabetic countries reviewed in Johansen still, the success of the antioxidants' treatment of diabetes in a clinical study is still missing, suggesting the need for exploration fastening on the connection between oxidative stress and diabetes- related pathological changes, in the final case, cell death. In that environment, ferroptosis has been examined in the last many times. Ferroptosis is a regulated, iron-dependent type of cell death whose backbone makes the cysteine/ glutamate exchanger (xCT)- glutathione (GSH)- glutathione peroxidase 4 (GPX4)- membrane hydroperoxide axis. As a cystine/glutamate transporter, xCT provides the cells with cysteine, a structure element of GSH that's "incorporated" into this patch in the response catalyzed by the rate- limiting enzyme glutamate- cysteine ligase (GCL) [2].

Under homeostatic conditions, oxidative damages being at the position of membrane lipids (therefore forming lipid peroxides) are instantly removed by the specific membrane- associated isoform of GPX, GPX4 which uses GSH as a reducing power. Still, if this antioxidant pathway becomes perturbed, membrane lipid peroxidation propagates throughout the membrane, compromising its integrity and eventually performing in cell death. Starting from the description of ferroptosis, interest in its involvement in colorful pathological surrounds is growing. To date, it has been reported that ferroptosis is involved in the development of diabetic metabolic complications, including renal injury, cognitive dysfunction, osteoporosis and endothelial and retinal injury. We've lately verified the recrimination of ferroptosis in diabetes etiology, as well. videlicet, we've set up that mimicking the diabetic terrain *in vitro* convinced β- cell death through ferroptosis. Also, our in vivo a generally used ferroptosis asset, bettered island morphology and functional status along with the drop in accumulation of lipid peroxides.

Then, we aimed to reveal the involvement of ferroptosis in diabetes-convinced pathological changes in the liver. For that purpose, we examined the goods of Fer-1 on ferroptosis- related parameters in the liver of mice with streptozotocin (STZ)- convinced diabetes. Fer-1 is one of the most potent ferroptosis impediments that exhibits high efficacity as radical- enmeshing antioxidants, with a particularly high energy in phospholipid bilayer membranes when compared to other antioxidants. Its metabolic conduct *in vivo* were considerably substantiated, and it's a well- established pharmacological tool for verification of ferroptosis [3].

### Fer-1 attenuates diabetes-induced liver damage

A statistically significant difference between the experimental groups was set up in the following parameters body mass, glycaemia, serum ALT and

TG position. A Tukey post hoc test revealed that the body mass of diabetic creatures was significantly dropped compared to the control group ($p<0.05$). Body mass of the Fer-1-treated diabetic group wasn't significantly different from both the control and diabetic group. Likewise, at day 21 of the trial, the mean serum glucose position was statistically advanced in diabetic creatures in comparison to the control ($p<0.01$). In diabetic creatures treated with Fer-1, glycemia was slightly lower than in the DM group but no significant difference was noted when compared to both the DM and Ctrl group. Regarding the hepatogram parameters, a significant elevation in the serum ALT position was set up in the diabetic group when compared to the control ($p<0.05$). The treatment with Fer-1 dropped ALT position compared to the DM group ($p<0.05$) and restored it towards the control position. TG position was increased in the DM group ($p<0.05$) in comparison to the control group and was restored with Fer-1 treatment, being lower when compared with the DM group ($p<0.05$) [4].

## Fer-1 improves diabetes-induced attenuation of gsh-related antioxidant defense in the liver

Changes in the GSH content and conditioning of GSH- related antioxidative enzymes are epitomized in Figure 3a. A significant difference among the groups in the content of GSH and exertion of GPX was set up in the liver being dropped in the DM group when compared to the control ($p<0.05$). Both GSH content and GPX exertion in the DM Fer-1 group returned to the control position and increased significantly compared to the DM group. Although there were no significant changes in GST exertion between the groups, there was a dwindling trend in the DM group compared to control, which faded in the DM Fer-1 group. GR exertion in the liver was also significantly different between the groups, and a post hoc test revealed that Fer-1 treatment of diabetic creatures increased exertion of GR compared with both the control and diabetic group ($p<0.01$ and $p<0.05$, independently) [5-10].

## Discussion

Cell death assumes a central part in the etiology of utmost liver pathologies, including those that are diabetes- related. We described, then, the ferroptotic phenotype in diabetic liver. All observed ferroptotic events increased accumulation ofpro-oxidative (similar as iron, lipofuscin, and 4-HNE) andpro-inflammatory (HMGB1) labels and drop in antioxidative defense- related motes (Nrf2, xCT, GSH, GPX4, GCL, HO-1, SOD) in the liver of diabetic creatures were lowered after the treatment with ferroptosis asset, Fer- 1. Similar salutary goods of Fer-1 were reflected in the normalization of diabetes- convinced differences in the liver metabolism (ALT and TG) and structure (lower fibrosis, unaltered hepatocytes size). Those changes convinced by Fer-1 in the liver of diabetic mice were bandied below.

The first pointers of the benefit of Fer-1 treatment on the diabetic liver were reclamations of biochemical labels and histology/morphology of the liver itself. The fact that Fer-1 dropped the diabetes- convinced increase in the position of ALT and TG suggests that ferroptosis indeed contributes to diabetes- related metabolic/ functional disturbances in the liver. These changes are further supported by histological analyses. Expansive deposit of collagen inside the extracellular matrix (fibrosis), a common index of liver damage in diabetic conditions, was reversed by Fer-1 treatment. Along with this, Fer-1 regularized hepatocytes size, morphology, and dropped the number of binuclear cells in the diabetic liver, a miracle which is reflective of liver rejuvenescence. Enlarged hepatocyte size in the diabetic liver could be a consequence of hepatocytes ' paragliding and/ or polyploidization which are both reflective of liver cell degeneration observed in the conditions including iron and bobby load and oxidative stress

## Conclusion

Our study revealed the ferroptotic phenotype of hepatocytes as an important part of the diabetic-convinced pathological changes in the liver. Also, the results suggest that targeting ferroptosis represents a new, promising approach in the forestallment and treatment of generally observed liver pathologies accompanying diabetes.

## Acknowledgement

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## Conflict of Interest

None.

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