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Exercise-Induced Lactate Is Associated with the Modulation of Mitophagy and Ferroptosis and Reduced Amyloid-Beta and Tau in Type 2 Diabetes

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ABSTRACT

Background: Type 2 diabetes (T2D) is associated with increased oxidative stress, impaired mitophagy, enhanced ferroptosis, and the accumulation of amyloid beta (Aβ) and hyperphosphorylated tau in the hippocampus. Exercise-induced lactate exerts neuroprotective effects via mitochondrial quality control and redox-regulating pathways. This study investigated whether high-intensity interval training (HIIT)-induced lactate accumulation can attenuate Aβ and tau pathology in diabetic rats by modulating mitophagy and ferroptosis-related protein signaling, as it remains unclear how HIIT-induced lactate impacts these pathways in T2D.

Methods: Thirty-two male Wistar rats were assigned to control (CO), exercise (EX), diabetes (DB), and diabetes + exercise (DB+EX) groups. T2D was induced using a high-fat diet and streptozotocin (35 mg/kg). The EX and DB+EX groups performed treadmill-based HIIT (4–10 intervals at 80–100% maximum running velocity). We measured serum lactate levels and the hippocampal protein levels of MCT2, SIRT1, BDNF, p62, Keap1, NRF2, MDA, GPX4, PINK1, parkin, Aβ, and Tau using standard laboratory methods.

Results: The DB group exhibited a significant increase in hippocampal oxidative stress markers and accumulation of Aβ and Tau compared to the control groups. In contrast, the DB + EX group showed elevated serum lactate levels and higher hippocampal protein levels of MCT2, SIRT1, BDNF, p62, NRF2, GPX4, PINK1, and Parkin. This group also demonstrated reduced levels of Keap1, MDA, Aβ, and Tau relative to the DB group.

Conclusion: HIIT enhanced mitophagy and reduced ferroptosis in the hippocampus of T2D rats, coinciding with the activation of lactate-SIRT1-BDNF and p62-Keap1-NRF2 pathways and reduced Aβ and Tau accumulation. ***DOI: 10.22034/IBJ.30.1.67***

Keywords: Ferroptosis, High-intensity interval training, Lactate, Mitophagy, Type 2 diabetes mellitus

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1. INTRODUCTION

Type 2 diabetes (T2D) is one of the most prevalent chronic diseases, with its incidence increasing at an alarming rate[1]. This systemic disease simultaneously impairs the function of multiple body systems, including the cardiovascular, digestive, immune, and nervous systems. Importantly, T2D is strongly associated with an increased risk of cognitive impairment and dementia[2]. Individuals with T2D are 1.5 to 2.5 times more likely to develop cognitive impairment, as its mild form affects approximately 45% of the patients[3].

Cognitive impairment in diabetes is driven by oxidative stress, which disrupts mitophagy and ferroptosis. Impaired mitophagy, a process that removes dysfunctional mitochondria, leads to mitochondrial accumulation and increased reactive oxygen species (ROS) generation. Key regulators of mitophagy, notably the PTEN-induced kinase 1 (PINK1)/Parkin pathway, are significantly compromised under conditions of oxidative stress. This compromise can manifest as reduced protein stability, impaired recruitment to damaged mitochondria, or decreased catalytic activity of these essential components, ultimately leading to a diminished capacity for mitophagy and the subsequent accumulation of dysfunctional mitochondria[4,5]. Hippocampal mitophagy dysfunction promotes the accumulation of amyloid beta (Aβ) and Tau proteins as key biomarkers of dementia-related disorders[6].

Oxidative stress, a key trigger of ferroptosis, drives iron-dependent lipid peroxidation and plays a significant role in mitochondrial dysfunction. Ferroptosis occurs alongside deficiencies in key redox enzymes, particularly glutathione peroxidase 4 (GPX4). In this context, agents such as RAS-selective lethal 3 (RSL3), erastin, and ferroptosis-inducing agent 56 (FIA56) disrupt the function of GPX4, a key regulator of ferroptosis, through distinct mechanisms. For instance, erastin inhibits cystine import via the xCT transporter, leading to glutathione depletion and subsequent GPX4 inactivation, while RSL3 directly inhibits GPX4 activity. These distinct upstream disruptions converge to ultimately impair GPX4's ability to neutralize lipid hydroperoxides, thereby triggering ferroptosis[7]. Such peripheral β-cell dysfunction promotes chronic hyperglycemia, insulin resistance, and systemic oxidative stress, which in turn exacerbate mitochondrial dysfunction, oxidative damage, and ferroptosis susceptibility in the hippocampus, thereby leading to diabetes-associated cognitive impairment[8-10].

Lactate, transported via monocarboxylate transporter 2 (MCT2), plays a critical role in ameliorating diabetes-induced cognitive impairments by promoting hippocampal neurogenesis[11,12]. Our previous study has shown that the elevated lactate levels and increased protein levels of MCT2 in hippocampal tissue contribute to cognitive improvements by activating sirtuin 1 (SIRT1), a key regulator of cellular metabolism and stress resistance, which enhances mitophagy and maintains mitochondrial quality[13]. Research has shown that exercise significantly alters the NAD^+/NADH ratio, which further increases SIRT1 levels in the brain. Additionally, lactate influences the beneficial effects of exercise on learning and memory by increasing the levels of brain-derived neurotrophic factor (BDNF) in the hippocampus through a SIRT1-dependent mechanism[14]. BDNF-mediated activation of nuclear factor erythroid 2-related factor 2 (NRF2) in astrocytes protects dopaminergic neurons from ferroptosis by enhancing antioxidant responses[15]. It seems that this protective effect could occur through the newly identified SIRT1-BDNF-p62-Keap1 (Kelch-like ECH-associated protein 1)-NRF2 signaling pathway, which enhances mitophagy and reduces ferroptosis, thus offering protection against diabetes-induced cognitive impairments.

Mitophagy and ferroptosis not only synergistically improve cognitive impairments but also have additive effects on overall cognitive function. Mitophagy reduces ROS and lipid peroxidation by clearing damaged mitochondria, preventing ferroptosis. However, impaired mitophagy leads to mitochondrial dysfunction, increasing ROS and iron release, which promotes ferroptosis. Conversely, ferroptosis, driven by iron overload and lipid peroxidation, can damage mitochondria and disrupt mitophagy signaling, which in turn worsens both processes. This action creates a feedback loop that exacerbates cellular damage, particularly in conditions like diabetes-induced cognitive decline and neurodegenerative diseases[16,17]. It seems that the increased protein levels of MCT2 play a more significant role than the mere elevation of lactate levels, particularly in the context of diabetes-related cognitive impairments. This is because MCT2, as a monocarboxylate transporter, is responsible for the uptake of lactate into neurons. While elevated systemic lactate is present, the efficient transport of lactate into specific neuronal populations, which provides crucial energy substrates and influences neurotransmission, relies on the availability and function of MCT2. In diabetes, impaired MCT2 function or altered protein levels may hinder this necessary intracellular lactate supply, leading to neuronal dysfunction and cognitive deficits, even if overall lactate levels are high. High-intensity interval training (HIIT) is a promising, non-invasive, and cost-effective method to acutely increase lactate levels and boost MCT2 protein levels[18]. The present study was designed to test the hypothesis that

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HIIT-induced lactate elevation is associated with the activation of the SIRT1-BDNF signaling axis in the hippocampus of type 2 diabetic rats, leading to the downstream modulation of mitophagy and ferroptosis-related pathways. Other molecular pathways examined in this study supported the mechanisms contributing to mitochondrial quality control and redox homeostasis rather than independent primary targets.

2. MATERIALS AND METHODS

This experimental animal study was conducted on 32 male Wistar rats, aged 8 weeks and weighing 200 ± 12 g on average. The rats were procured from the Animal Facility of Kerman University of Medical Sciences, Kerman, Iran. The animals were housed in polycarbonate cages under controlled environmental conditions, including a temperature of 22 ± 2°C, relative humidity of 50 ± 4%, and a 12-hour light/dark cycle. Food and water were provided ad libitum throughout the study period. For Western blot analysis, we used the following antibodies: MCT2 (sc-166925), BDNF (sc-2392), p62 (SQSTM1/p62 antibody (A-6); sc-48402), INK1 (sc-133197), Parkin (sc-32282), and Aβ (sc-28365), all from Santa Cruz Biotechnology, USA, and SIRT1 (AB189494), Keap1 (AB139729), NRF2 (AB76026), GPX4 (AB252833), and hyperphosphorylated tau protein (Tau [phospho T231], ab151559), all from Abcam, UK.

2.1. Animal grouping

Animals were first acclimatized to the laboratory environment for one week. Subsequently, they were randomly assigned into four groups, each comprising eight rats: (i) CO (control), (ii) EX (exercise), (iii) DB (T2D), and (iv) DB + EX (T2D combined with exercise).

2.2. T2D induction

During the first eight weeks of the study, the rats in the DB and DB + EX groups were maintained on a high-fat diet consisting of 60% fat, 20% protein, and 20% carbohydrate to induce metabolic changes. At the end of this period, the animals underwent a 12-hour fast, followed by a single intraperitoneal injection of streptozotocin (STZ) at a dose of 35 mg/kg to induce diabetes. Three days after STZ administration, fasting blood glucose (FBG) levels were measured using a glucometer[19-21].

2.3. Exercise protocol

To prepare the rats for treadmill exercise, we implemented a five-day acclimatization period. During this phase, the rats ran on a treadmill daily at a constant speed of 8 m/min for 10 minutes. After completing this adaptation period, an incremental treadmill test was conducted to assess the maximum running velocity (V_{max}) for each rat. The test started at a speed of 6 m/min, maintained for 2 minutes, and the treadmill speed was then increased by 2 m/min every 2 minutes until the rats reached exhaustion. The highest speed maintained by the rats before exhaustion was recorded as their V_{max}. Subsequently, the training protocol was adjusted every two weeks based on the updated V_{max} values. The details of the exercise protocol are presented in Table S1.

2.4. Exhaustion index and determination of V_{max}

To evaluate aerobic capacity and running performance in rats, we employed an incremental treadmill protocol. The exhaustion index was defined as the animal's inability to continue running despite being manually repositioned on the treadmill three consecutive times after reaching the end of the belt. Specifically, if a rat stopped running and was displaced to the end of the treadmill, the researcher gently placed it back at the front of the belt. If the animal failed to resume running after three successive attempts, it was considered exhausted. In such cases, the speed corresponding to the last fully completed running stage was recorded as the V_{max}. This approach provides an objective and reproducible criterion for determining exercise termination and physical performance in animal models.

2.5. Sampling

2.5.1. Blood sample

Forty-eight hours after the final training session, the rats were euthanized under anesthesia, which was administered via intraperitoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg). Blood samples were then collected directly from the heart and centrifuged at 1000 ×g at 4°C for 20 minutes. The resulting serum was aliquoted and stored at -80°C until further analysis[22].

2.5.2. Hippocampus sample

Hippocampal tissue was carefully dissected and rinsed with phosphate-buffered saline to remove debris. The tissue was then homogenized on ice using an ultrasonic homogenizer in RIPA buffer containing a protease inhibitor cocktail to prevent protein degradation. The homogenate was subjected to centrifugation at 13,229 ×g at 4°C for 20 minutes to separate cellular components. The resulting supernatant was collected and immediately stored at -80°C for later biochemical analyses. To minimize the potential effects of circadian rhythm on protein levels, particularly for rhythmic markers such as BDNF and NRF2, all tissue samples were collected between 08:00 and 13:00. This

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standardized time window was selected to ensure consistency across experimental groups and to reduce diurnal variability. consistency across experimental groups and to reduce diurnal variability.

2.6. ELISA

Lactate concentration in serum and hippocampus was quantified using the enzymatic lactate assay kit (Abcam), while insulin levels in serum and hippocampus were measured using the Rat Insulin ELISA Kit (Crystal Chem Inc., Elk Grove Village, IL, USA), following each manufacturer's protocol. Blood was collected and centrifuged in a refrigerated centrifuge at 4°C to separate the serum while preventing enzyme and protein degradation. To inhibit protein breakdown, we used a protease inhibitor solution containing 0.5 mM phenylmethylsulfonyl fluoride. After centrifugation, the supernatant was carefully collected, and lactate concentrations were measured by an ELISA reader (Bio-Rad, USA). The results were reported as nanograms of lactate per milligram of protein, utilizing the Rat.

2.7. Western blotting

The protein levels of MCT2, SIRT1, BDNF, p62, Keap1, Nrf, GPX4, PINK1, Parkin, Aβ, and hyperphosphorylated tau protein were measured using the Western blotting technique. Samples were prepared, and the target proteins were separated via gel electrophoresis before being transferred onto nitrocellulose membranes (0.45 μm pore size) at a current of 0.5 Amps for 1.5 hours. The gel was pre-incubated in the transfer buffer for at least 10 minutes after trimming the compacting region. Nitrocellulose membranes and filter pads, cut to precise dimensions, were assembled into a blotting sandwich and secured within a plastic frame. The assembly was then immersed in a transfer buffer-filled blotting tank. The membranes were incubated with primary antibodies, diluted at 1:1000, for 16–18 hours. After incubation with horseradish-conjugated secondary antibodies (1:5000), protein bands were detected using a standard chemiluminescent substrate and visualized with the ChemiDoc XRS + imaging system (Bio-Rad). The bands were then quantified using ImageJ software. Beta-actin served as the internal control for normalization during the analysis.

2.8. Malondialdehyde (MDA) determination in hippocampus

MDA, a product of membrane lipid peroxidation, was quantified as a marker of oxidative stress using the thiobarbituric acid assay. Hippocampal tissue was homogenized in cold physiological saline, followed by centrifugation at 78 ×g for 10 minutes to obtain the supernatant. To do the assay, 20 μL of the supernatant was mixed with 150 μL of thiobarbituric acid, 20 μL of sodium dodecyl sulfate, 150 μL of 20% acetic acid (pH 3.5), and 60 μL of distilled water. The reaction mixture was incubated at 90°C for 45 minutes, then cooled to room temperature for 10 minutes. After cooling, the mixture was centrifuged at 10,000 ×g to obtain a clear supernatant. The absorbance of the solution was measured at 532 nm. Tetramethoxypropane was used to generate a standard curve at concentrations of 2.5, 5, 10, 20, 30, 40, and 50 nmol/mL. MDA levels were quantified in nanomoles per milliliter based on the standard curve[23].

2.9. Assessment of insulin resistance/sensitivity indices

To evaluate insulin resistance, we used two different indices: the homeostasis model assessment of insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI). The HOMA-IR was calculated using the formula: HOMA-IR = [(fasting glucose (mmol/L) × fasting insulin (μU/mL))/22.5], a method commonly employed to assess the degree of insulin resistance based on fasting glucose and insulin levels. This index provides an estimate of the body's ability to regulate blood glucose levels in relation to insulin secretion. Additionally, the QUICKI method was utilized due to its superior linear correlation with insulin sensitivity as measured by glucose clamp techniques, which are considered the gold standard for assessing insulin sensitivity. QUICKI is calculated using the formula proposed by Katz et al.[24] which is expressed as: QUICKI = 1/[log (fasting insulin in μU/mL) + log (fasting glucose in mg/dL)]. This index is particularly valuable as it provides a simple, reliable, and accurate measure of insulin sensitivity, reflecting how the body effectively uses insulin to control blood glucose levels under fasting conditions. Both of these indices offer insights into the metabolic status of the individual, specifically regarding their insulin sensitivity and resistance[25].

2.10. Statistical analysis

All statistical analyses were conducted using GraphPad Prism 10 software, ensuring accurate data interpretation and visualization. The normality of the data distribution was assessed using the Shapiro-Wilk test, and Levene's test was applied to examine the homogeneity of variances across groups. Depending on the data distribution and variance homogeneity, either a one-way analysis of variance (ANOVA) followed by standard post-hoc tests (e.g., Tukey) or the non-parametric Kruskal-Wallis test followed by Dunn's post-hoc test was conducted to compare differences among the groups. Results were reported as mean ±

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standard error of the mean. Statistical significance was considered at a p value of less than 0.05.

3. RESULTS

3.1. Normality and homogeneity Tests

Our normality and homogeneity tests revealed distinct requirements for statistical analysis: parametric methods are applicable to FBG, body weight, insulin, HOMA-IR/QUICKI, lactate, and MDA, while non-parametric methods are necessary for MCT2, SIRT1, BDNF, p62, Keap1, NRF2, GPX4, PINK1, Parkin, Aβ, and Tau variables.

3.2. Effects of diabetes induction and exercise on metabolic parameters

One-way ANOVA revealed a significant difference among the experimental group regarding FBG ($F(3,28) = 239.27$; $p < 0.001$; $\eta^2 = 0.967$), body weight ($F(3,28) = 120.19$; $p < 0.001$; $\eta^2 = 0.94$), and serum insulin levels ($F(3,28) = 177.32$; $p < 0.001$; $\eta^2 = 0.960$). Post hoc analysis demonstrated a significant elevation in FBG levels ($t(14) = 10.3$; $p < 0.001$), body weight ($t(14) = 8.9$; $p < 0.001$), and insulin levels ($t(14) = -6.2$; $p < 0.001$) in the DB group compared to the CO group. In contrast, the exercise EX group exhibited significantly lower FBG levels ($t(14) = -6.8$; $p < 0.001$) and body weight ($t(14) = -5.8$; $p < 0.001$) relative to the CO group. Furthermore, the DB + EX group showed a substantial reduction in FBG ($t(14) = -7.5$; $p < 0.001$) and body weight ($t(14) = -6.3$; $p < 0.001$) concentrations compared to the DB group. However, this trend was reversed for serum insulin levels ($t(14) = 6.4$; $p < 0.001$; Table 1). Significant differences in QUICKI levels were identified across the experimental groups ($F(3,28) = 81.57$; $p < 0.001$; $\eta^2 = 0.9$), reflecting a pronounced effect of the interventions. Post hoc analyses revealed a significant reduction in QUICKI in the DB group compared to the CO group ($t(14) = 7.4$; $p < 0.001$). Moreover, the DB + EX group exhibited significantly lower HOMA-IR levels compared to the DB group ($t(14) = -6.0$; $p < 0.01$; Table 1).

3.3. Serum lactate and hippocampal MCT2, SIRT1, and BDNF levels

Analysis revealed significant differences among the experimental groups regarding Lactate-S levels ($F(3,28) = 138.09$; $p < 0.001$; $\eta^2 = 0.94$). Post hoc comparisons indicated that the DB group had significantly higher Lactate-S protein levels compared to the CO group ($t(14) = 8.7$; $p < 0.001$), and the DB + EX group also differed significantly from the DB group ($t(14) = 7.8$; $p < 0.001$). No significant difference was observed between the CO and EX groups (Fig. 1). Similarly, analysis revealed a statistically significant variation in MCT2 protein levels across the experimental groups ($H(3) = 29.55$; $p < 0.001$; $\varepsilon^2 = 0.86$). Bonferroni-adjusted post hoc comparisons demonstrated a significant decrease in MCT2 protein levels in the DB group compared to the CO group ($z = -3.44$; $p < 0.001$). Moreover, MCT2 protein levels significantly increased

Table 1. Body weight, FBG, serum insulin, and HOMA-IR in experimental groups (mean ± SD) at baseline, post-diabetes induction, and after HIIT (n = 8)

Parameter	Groups	Before starting intervention (month 0)	After DB induction (month 2)	After training (month 4)
Body Weight (g)	CO	156 ± 4	183 ± 12	199 ± 13
	DB	154 ± 6	249 ± 8***	257 ± 9**
	EX	155 ± 5	181 ± 12	167 ± 8
	DB + EX	157 ± 5	261 ± 18$^{\#\#\#}$	223 ± 11$^{\#}$
FBG (mg/dl)	CO	225 ± 4	221 ± 7	224 ± 6
	DB	223 ± 9	382 ± 13***	359 ± 17***
	EX	224 ± 7	219 ± 5	208 ± 11
	DB + EX	227 ± 5	394±14***	303 ± 9$^{\#\#\#}$
Serum insulin (ng/mL)	CO	3.5 ± 0.1	3.6 ± 0.2	3.7 ± 0.3
	DB	3.5 ± 0.1	4.3 ± 0.4***	4.6 ± 0.2**
	EX	3.5± 0.1	3.6 ± 0.2	1.6 ± 0.2
	DB + EX	3.6 ± 0.1	4.5 ± 0.3*	2.5 ± 0.3$^{\#\#}$
HOMA-IR	CO	48 ± 3	54 ± 2	56 ± 4
	DB	42 ± 5	81 ± 6***	88 ± 5***
	EX	45 ± 4	56 ± 5	39 ± 29
	DB + EX	46 ± 6	91 ± 5***	67 ± 89$^{\#\#}$

CO: control; DB: type 2 diabetic (STZ injected); EX: exercise only; DB + EX: type 2 diabetic + exercise; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. CO. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ vs. T2D.

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in the DB + EX group compared to the DB group (z = 3.44; $p < 0.001$; Fig. 1). SIRT1 protein levels differed significantly among the groups (H(3) = 29.55; $p < 0.001$; $\varepsilon^2 = 0.86$). Bonferroni-adjusted post hoc analysis revealed a marked downregulation of SIRT1 in the DB group compared to the CO group (z = -3.44; $p < 0.001$). However, SIRT1 protein levels in the EX-group did not significantly differ from those in the CO group. Furthermore, a significant upregulation of SIRT1 was observed in the DB + EX group compared to the DB group (z = 3.44; $p < 0.001$) (Fig. 1). Similarly, a significant difference in BDNF protein levels was observed among the experimental groups (H(3) = 29.55, $p < 0.001$; $\varepsilon^2 = 0.86$). Bonferroni-adjusted post hoc analysis revealed a significant downregulation of BDNF protein levels in the DB group compared to the CO group (z = -3.44; $p < 0.001$). Additionally, the EX-group showed a significant increase in BDNF protein level relative to the CO group (z = -1.719; $p < 0.001$). Furthermore, a significant increase in BDNF protein levels was observed in the DB + EX group compared to the DB group (z = 3.44; $p < 0.001$; Fig. 1).

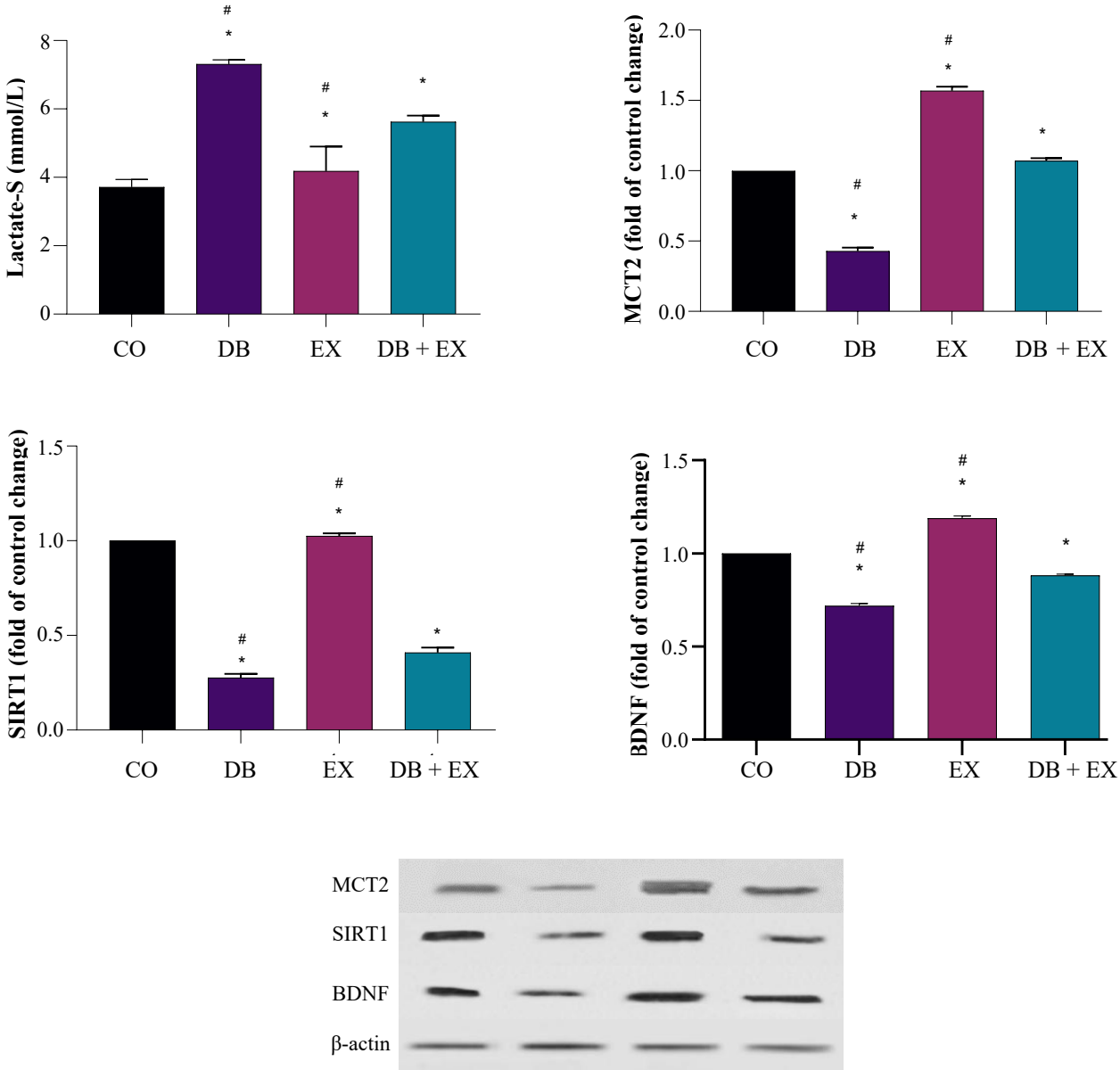

Fig. 1. Protein levels of lactate in serum, MCT2, SIRT-1, and BDNF in hippocampus (n = 8 in each group). CO: control; DB: type 2 diabetic; EX: exercise; DB + EX: type 2 diabetic + exercise; $^{*}p < 0.001$ shows a significant difference compared to other groups and $^{\#}p < 0.001$ with the DB + EX group.

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3.4. Hippocampal p62, Keap1, and NRF2 protein levels

A significant difference in p62 (H(3) = 28.25; $p < 0.001$; $\varepsilon^2 = 0.84$), Keap1 (H(3) = 28.25; $p < 0.001$; $\varepsilon^2 = 0.82$), and NRF2 (H(3) = 26.96; $p < 0.001$; $\varepsilon^2 = 0.80$) protein levels were observed among the experimental groups. Bonferroni-adjusted post hoc analysis revealed a significant downregulation of p62 (z = -3.65; $p < 0.001$), Keap1 (z = -3.22; $p < 0.001$), and NRF2 (z = -3.44; $p < 0.001$) protein levels in the DB group compared to the CO group. Additionally, the EX group exhibited a significant increase in p62 (z = -1.289; $p < 0.001$), Keap1 (z = 1.934; $p < 0.001$), and NRF2 (z = -1.289; $p < 0.01$) protein levels relative to the CO group (Fig. 2). A statistically significant variation in Keap1 protein level was identified among the experimental groups (H(3) = 28.25; $p < 0.001$; $\varepsilon^2 = 0.82$). Bonferroni-adjusted post hoc analysis revealed a significant downregulation of Keap1 protein levels in the DB group compared to the CO group (z = −3.22; $p < 0.001$). In contrast, Keap1 protein levels were significantly upregulated in the EX group compared to the CO group (z = 1.934; $p < 0.001$). Moreover, the DB + EX group showed a significant increase in Keap1 protein levels compared to the DB group (z = 3.22; $p < 0.001$; Fig. 2). Protein levels of NRF2 varied significantly among the experimental groups (H(3) = 26.96; $p < 0.001$; $\varepsilon^2 = 0.80$). Bonferroni-adjusted post hoc comparisons demonstrated a pronounced downregulation of NRF2 protein levels in the DB group relative to the CO group (z = -3.44; $p < 0.001$). Furthermore, the EX-group exhibited a significant increase in NRF2 protein levels compared to the CO group (z = -1.289; $p < 0.01$). Notably, a significant upregulation of NRF2 protein levels was detected in the DB + EX group when compared to the DB group (z = 3.44; $p < 0.01$; Fig. 2).

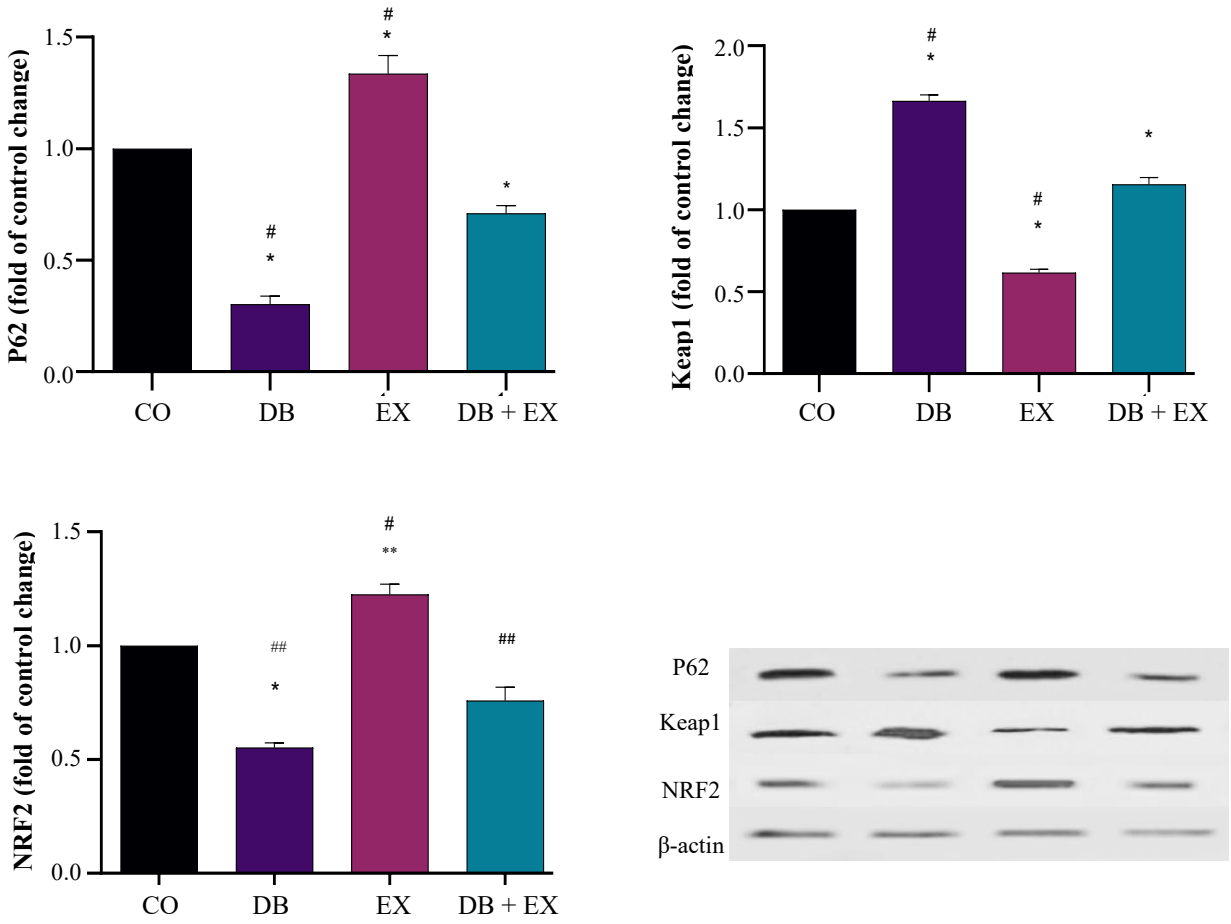

Fig. 2. Protein levels of p62, Keap1, and NRF2 hippocampus (n = 8 in each group). CO: control; DB: type 2 diabetic; EX: exercise; DB + EX: type 2 diabetic + exercise. $^{*}p < 0.001$ indicates significant differences with other groups, $^{\#}p < 0.001$ with the DB + EX group, $^{**}p < 0.01$ between EX and CO, and $^{\#\#}p < 0.01$ between DB + EX and DB.

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3.5. Hippocampal GPX4 protein and MDA levels

GPX4 protein levels varied significantly among the experimental groups ($H(3) = 28.99$; $p < 0.001$; $\varepsilon^2 = 0.83$), reflecting a substantial impact of the experimental interventions. Bonferroni-adjusted post hoc analysis indicated a significant downregulation of GPX4 protein levels in the DB group compared to the CO group ($z = -3.33$; $p < 0.001$). However, the EX group showed a marked increase in GPX4 protein levels relative to the CO group ($z = -1.834$; $p < 0.001$). Moreover, a significant upregulation of GPX4 protein levels was observed in the DB + EX group compared to the DB group ($z = 3.33$; $p < 0.001$; Fig. 3). One-way ANOVA revealed a statistically significant difference in MDA levels among the experimental groups ($F(3,28) = 39.77$; $p < 0.001$; $\eta^2 = 0.810$), indicating a substantial effect of the experimental conditions on lipid peroxidation. Post hoc analyses demonstrated a significant increase in MDA amount in the DB group compared to the CO group ($t(14) = 5.6$; $p < 0.001$). In contrast, the DB + EX group exhibited a marked reduction in MDA levels relative to the DB group ($t(14) = -5.1$; $p < 0.001$; Fig. 3).

3.6. Hippocampal PINK1 and Parkin protein levels

The protein levels of PINK1 differed significantly across the experimental groups ($H(3) = 27.33$; $p < 0.001$; $\varepsilon^2 = 0.82$), suggesting a substantial modulatory effect of the experimental conditions on its regulation. Bonferroni-adjusted post hoc analysis revealed a pronounced downregulation of PINK1 protein levels in the DB group compared to the CO group ($z = -3.87$; $p < 0.001$). In contrast, the PINK1 protein levels in the EX group were not significantly different from those observed in the CO group. Notably, the DB + EX group exhibited a significant restoration of PINK1 protein levels compared to the DB group ($z = 3.87$; $p < 0.001$), with protein levels comparable to those in the CO group (Fig. 4). Furthermore, significant differences in Parkin protein levels were detected across the experimental groups ($H(3) = 29.55$; $p < 0.001$; $\varepsilon^2 = 0.86$), demonstrating a pronounced effect of the mitophagy interventions. Based on Bonferroni-adjusted post hoc comparisons, we observed a marked downregulation of Parkin protein levels in the DB group compared to the CO group ($z = -3.44$; $p < 0.001$). Conversely, the EX group exhibited a significant upregulation relative to the CO group ($z = -3.438$; $p < 0.001$). Furthermore, Parkin protein levels were significantly reduced in the DB + EX group compared to the DB group ($z = 3.44$; $p < 0.001$; Fig. 4).

3.6 Hippocampal Aβ and Tau protein levels

The results of the Kruskal–Wallis test demonstrated a statistically significant difference in AB protein levels among the experimental groups ($H(3) = 29.55$; $p < 0.001$; $\varepsilon^2 = 0.86$), indicating a substantial effect of the interventions on AB protein levels. Bonferroni-adjusted post hoc analyses revealed a significant downregulation of AB protein levels in the EX group compared to the CO group ($z = 1.719$; $p < 0.001$). Conversely, AB protein levels were significantly upregulated in the DB group relative to the CO group ($z = 3.44$; $p < 0.001$). Furthermore, a significant decrease in AB protein levels was observed in the DB + EX group compared to the DB group ($z = -3.44$; $p < 0.001$; Fig. 5). Finally, a statistically significant difference in Tau protein levels was observed among the

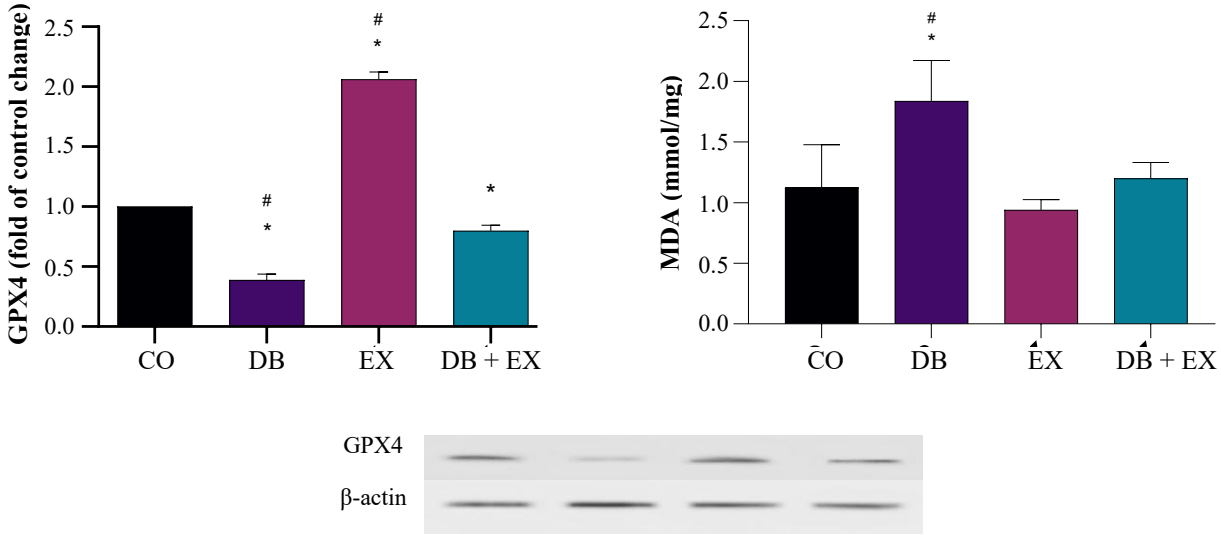

Fig. 3. Protein levels of GPX4 and MDA in hippocampus (n = 8 in each group). CO: control; DB: type 2 diabetic; EX: exercise; DB + EX: type 2 diabetic + exercise. $^{*}p < 0.001$ shows significant differences compared to other groups and $^{\#}p < 0.001$with the DB + EX group.

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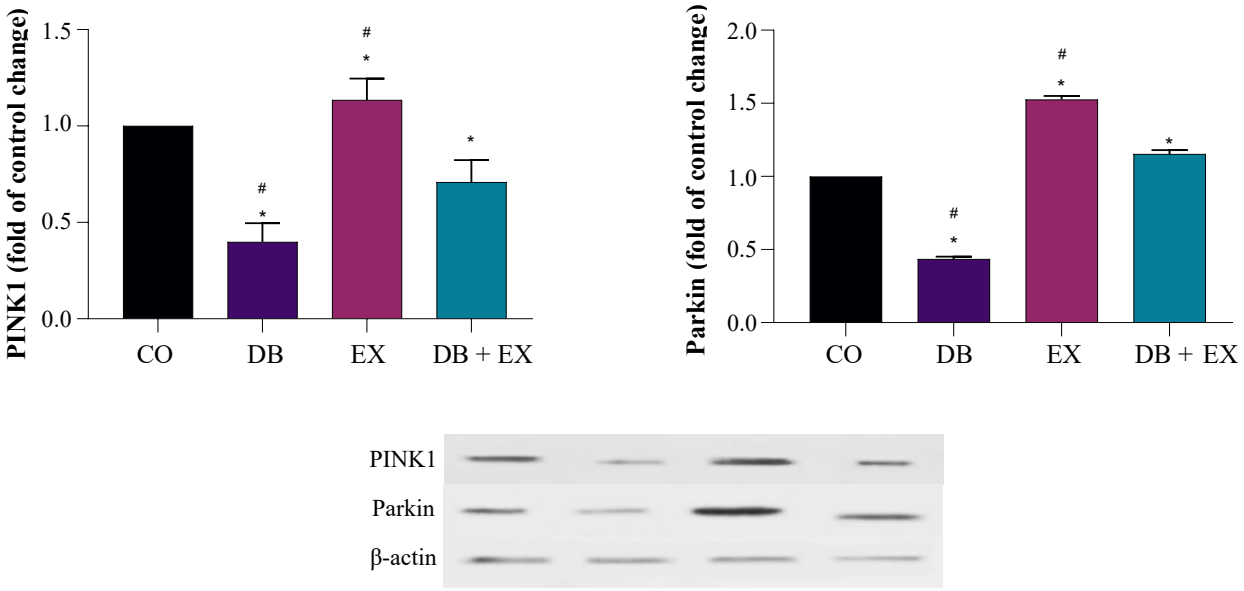

Fig. 4. PINK1 and Parkin levels in hippocampus (n = 8 in each group). CO: control; DB: type 2 diabetic; EX: exercise; DB + EX: type 2 diabetic + exercise; $^{*}p < 0.001$ shows significant differences compared to other groups and $^{\#}p < 0.001$with the DB + EX group.

experimental groups (H(3) = 29.55; $p < 0.001$; $\varepsilon^2 = 0.86$), indicating a pronounced effect of the interventions on Tau protein levels. Bonferroni-adjusted post hoc comparisons revealed a significant downregulation of Tau protein levels in the EX group relative to the CO group (z = 3.44; $p < 0.001$). Conversely, Tau protein levels were significantly upregulated in the DB group compared to the CO group (z = 1.719; $p < 0.001$). Additionally, a significant decrease in Tau protein levels was found in the DB + EX group relative to the DB group (z = -3.44; $p < 0.001$; Fig. 5).

4. DISCUSSION

Diabetes is strongly linked to increased oxidative stress, disrupted cellular homeostasis, and impaired mitophagy, particularly via the PINK1-Parkin pathway[26]. This disruption hinders mitochondrial quality control, leading to cellular dysfunction. Furthermore, diabetes promotes ferroptosis, a regulated form of cell death driven by lipid peroxidation, primarily through the downregulation of GPX4. These processes exacerbate neuronal damage and are associated with cognitive decline, marked by the accumulation of abnormal Tau protein and amyloid-beta plaques[8-10]. These diabetes-induced abnormalities are effectively mitigated by reducing oxidative stress and restoring mitophagy through the PINK1-Parkin pathway, as well as inhibiting ferroptosis via enhanced GPX4 activity. This metabolic reprogramming is also associated with a reduction in the levels of Aβ and Tau[27].

Oxidative stress significantly impairs mitophagy by disrupting the PINK1-Parkin signaling pathway. Normally, damaged mitochondria stabilize PINK1 on the outer mitochondrial membrane, which recruits Parkin to facilitate mitophagy. However, oxidative stress either overwhelms the mitophagy system or directly suppresses the protein levels and activity of key proteins, such as PINK1 and Parkin, which are critical for the mitophagy process. Zhang et al. have shown that high ROS levels hinder PINK1-Parkin recruitment, resulting in the accumulation of dysfunctional mitochondria in neuronal cells and contributing to neurodegeneration[28]. Similarly, Wang et al. have also indicated that oxidative stress induces modifications in the mitochondrial membranes that hinder mitophagosome formation, further exacerbating mitochondrial damage[29]. Conversely, some studies have suggested that moderate levels of oxidative stress may act as a signal for mitophagy initiation rather than its suppression[30-32]. For example, it has been argued that ROS act as signaling molecules that enhance PINK1 stabilization and promote mitophagy under specific physiological conditions, particularly following treatment with mitochondrial uncoupling agents such as carbonyl cyanide m-chlorophenyl hydrazone or through increased protein levels of voltage-dependent anion channel 1, both of which induce mitochondrial depolarization and facilitate the accumulation of PINK1 on the outer mitochondrial membrane[26]. On the other hand, diabetes significantly contributes to the induction of ferroptosis, a regulated form of cell death

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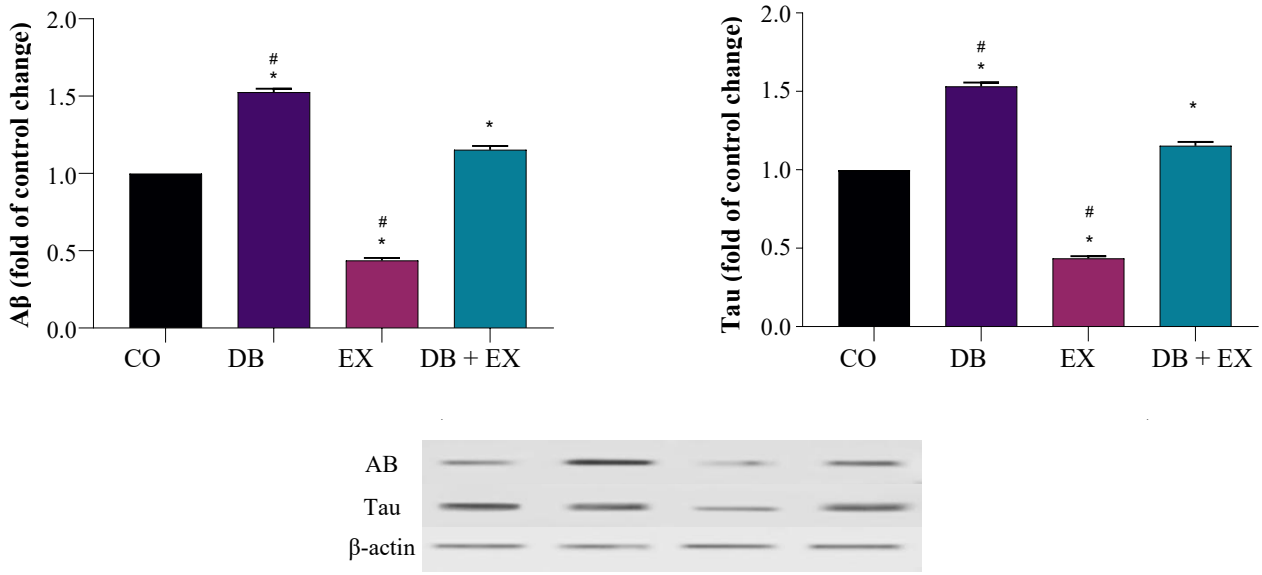

Fig. 5. Protein levels of Aβ and Tau in hippocampus (n = 8 in each group). CO: control; DB: type 2 diabetic; EX: exercise; DB + EX: type 2 diabetic + exercise; significant difference compared to other groups ($^{*}p < 0.001$) and the DB+EX group ($^{\#}p < 0.001$).

characterized by iron-dependent lipid peroxidation. This process is closely linked to oxidative stress, as excessive ROS generated in diabetes disrupts cellular homeostasis and accelerates lipid peroxidation. Ferroptosis is primarily driven by the depletion of glutathione and inactivation of GPX4, key antioxidants that prevent lipid membrane damage[7]. Elevated ROS levels suppress GPX4 activity and deplete intracellular glutathione stores, triggering ferroptotic pathways. This oxidative stress-mediated ferroptosis contributes to the progression of diabetic complications, including neurodegeneration and cardiovascular dysfunction[27]. Fang et al. have demonstrated that ROS-induced ferroptosis exacerbates cardiac damage in diabetes by promoting lipid peroxidation and iron accumulation. Their findings suggest that ferroptosis inhibitors, such as liproxstatin-1, significantly reduce diabetic cardiomyopathy by restoring GPX4 activity and decreasing lipid peroxidation[33]. Li et al. have shown that HIIT improves memory and learning in type 2 diabetic mice by enhancing mitophagy in the hippocampus. HIIT increased Beclin-1 levels, LC3-II/I ratio, and decreased p62 protein levels, indicating improved autophagy. Compared to moderate-intensity training, HIIT exerted a greater inhibitory effect on the PI3K/Akt/mTOR pathway, indicating its superior potential in improving hippocampal function and cognitive outcomes in diabetes[34]. In line with these findings, Freitas et al. have demonstrated that six weeks of HIIT reduces oxidative stress and inflammation in the hippocampus while increasing BDNF levels in rats[35]. HIIT reduces pro- and anti-inflammatory cytokines, attenuates lipid peroxidation, and enhances antioxidant defenses, thereby mitigating oxidative stress and improving mitochondrial function. These adaptations are largely mediated by lactate accumulation and MCT2 upregulation[35]. These molecular responses trigger several signaling pathways, including the activation of SIRT1, BDNF[36], and the p62-KEAP1-NRF2 pathway, ultimately leading to the increased mitophagy and decreased ferroptosis[37].

Previously thought to be just a metabolic waste product, lactate produced during intense exercise is now understood to act as a key signaling molecule. When lactate is transported into cells via MCT2, it activates several downstream signaling pathways, including the upregulation of SIRT1[13,38]. SIRT1 is involved in mitochondrial biogenesis and the regulation of oxidative stress. Supporting evidence shows that lactate acts as a potent activator of SIRT1. Hoshino et al. have demonstrated that lactate enhances SIRT1 activity, which subsequently increases mitochondrial turnover and oxidative stress resistance[39]. Furthermore, Qiu et al. have highlighted that lactate-induced activation of SIRT1 can stimulate mitochondrial biogenesis, leading to a reduction in ROS production[40]. SIRT1 activation by lactate also contributes to the upregulation of BDNF, which plays a critical role in neuronal survival, synaptic plasticity, and cognitive function. Both are influenced by increased lactate levels, contributing to improvements in cognitive disorders and the regulation of ferroptosis in the hippocampus[14,41]. Our findings

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support the notion that HIIT-induced lactate elevation is associated with enhanced SIRT1 and BDNF protein levels (Fig. S1). BDNF has been linked to mitochondrial health, as it promotes mitochondrial biogenesis and supports mitophagy[42].

BDNF can enhance p62 protein levels, which plays a protective role in neurons by mitigating mitochondrial dysfunction and safeguarding against functional impairments[43]. It has been shown that BDNF upregulation enhances the P62, which in turn boosts the protein levels of Keap1 and NRF2[43]. The phosphorylation of p62 activates the Keap1-NRF2 pathway, playing a critical role in selective autophagy[44]. NRF2 is a master regulator of cellular antioxidant defenses[45]. p62 enhances NRF2 activity by enzyme activity, suggesting that HIIT promotes a neuroprotective environment and supports hippocampal function[46]. HIIT has been shown to bind to Keap1, while NRF2 increases p62 protein levels, forming a feedback mechanism. This pathway regulates mitochondrial quality by coordinating biogenesis and mitophagy, making it essential for protecting against oxidative stress and maintaining cellular stability[47].

Our data indicate that upregulation of BDNF is associated with the enhanced activation of the antioxidant P62-KEAP1-NRF2 signaling pathway (Fig. S1). In the DB + EX group, the levels of these factors were significantly elevated compared to the DB group. Exercise-induced lactate elevation is associated with activation of pathways such as SIRT1, BDNF, and P62-Keap1-NRF2, which improve mitophagy. In diabetes, mitophagy helps improve mitochondrial function and reduce oxidative damage, as shown by some researchers[48,49]. Also, lactate-induced activation of SIRT1 and BDNF can enhance PINK1-Parkin-mediated mitophagy, leading to improved mitochondrial health and reduced oxidative damage[13,14]. In parallel, the upregulation of antioxidants via the P62-Keap1-NRF2 pathway can help reduce ferroptosis by enhancing GPX4 activity[10].

Mitophagy and ferroptosis are interconnected processes influencing cell fate under stress. Mitophagy prevents. Previously thought to be just a metabolic waste product, lactate produced during intense exercise is now understood to act as a key signaling molecule by removing damaged mitochondria, thereby reducing oxidative stress and lipid peroxidation[40]. Conversely, impaired mitophagy leads to mitochondrial dysfunction, elevated ROS levels, and ferroptosis. It has been suggested that enhanced mitophagy can mitigate ferroptosis in neuronal cells by reducing mitochondrial damage, oxidative stress, and lipid peroxidation (Fig. S1). Activation of mitophagy may prevent ferroptosis in neurons by reducing oxidative stress. It also decreases the accumulation of toxic proteins such as tau and Aβ, which are linked to cognitive dysfunction. Enhancing mitophagy could, therefore, be a potential strategy to protect neurons from damage, inhibit ferroptosis, and reduce tau and Aβ, ultimately delaying cognitive dysfunction[50]. Our results showed a significant decrease in AB and Tau levels in the DB + EX group compared to the DB group.

Because the study did not include a control group receiving exogenous lactate apart from HIIT, it's challenging to distinguish the specific effects of lactate from those of the exercise protocol. However, the observed differences in serum and hippocampal lactate levels, along with the hippocampal to serum MCT2 values, provide some ability to mitigate this limitation in the results. Our focus was on exercise-induced lactate, and due to financial constraints, we could not add an additional group. This limitation should be addressed in future mechanistic studies. Another limitation of this study is the lack of behavioral assessments to directly evaluate cognitive function. Although a reduction in Aβ and Tau levels suggests potential neuroprotective effects, the absence of functional memory tests limits the translational interpretation. Due to insufficient access to behavioral testing equipment, we were unable to include such evaluations, which should be addressed in future research. While we measured the protein levels of MDA and GPX4 as two important indicators of ferroptosis, financial limitations prevented us from assessing other ferroptosis-related factors such as iron accumulation, ACSL4 protein levels, and lipid ROS. This limitation may restrict the strength of the conclusion regarding ferroptosis.

6. CONCLUSION

The present study reveals an association among oxidative stress, mitophagy indices, and ferroptosis markers in diabetes-related cognitive dysfunction. We observed the patterns that are consistent with disrupted mitochondrial quality control (lower PINK1-Parkin), increased ferroptosis susceptibility (reduced GPX4), and high Aβ/Tau levels alongside oxidative damage in the diabetic rats. Meanwhile, eight weeks of HIIT coincided with lower oxidative stress markers, elevated mitophagy-related proteins, reduced ferroptosis indices, and decreased Aβ/Tau levels. These changes occurred together with elevated serum lactate and hippocampal shifts in SIRT1, BDNF, and p62-KEAP1-NRF2 protein levels. Importantly, this correlative design cannot establish causality, as we lack targeted interventions (pharmacological or genetic) to dissect the lactate-SIRT1-BDNF axis or downstream pathways. Future mechanistic studies are needed to confirm these relationships.

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DECLARATION

Acknowledgments
Not applicable.

Generative AI and AI-assisted technologies
We used ChatGPT to improve the clarity and overall readability of their manuscripts.

Ethical approval
The study protocols were approved by the Animal Care and Ethics Committee of Kerman University of Medical Sciences (KUMS), Kerman, Iran (ethical code: IR.UK.REC.1400.447).

Consent to participate
Not applicable.

Consent for publication
All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions
PK: conceptualization, methodology, software, formal analysis, investigation, data curation, writing original draft, preparation; FS: writing-review & editing, methodology, supervision; AE: supervision, formal analysis, writing-review & editing; KK: methodology, validation, resources, data curation, writing-review & editing, supervision, administration, funding acquisition.

Data availability
All relevant data can be found within the manuscript.

Competing interests
The authors declare that they have no competing interests.

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Supplementary information
The online version does contain supplementary material.

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