

**The effect of endurance training on weight changes,
serum glucose levels, and NLRP-1 protein expression in
the hippocampus of male rats with diabetes**

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How to Cite: Ahadiyan, M; Karimjuzani, M. & Ahmadpour Torkamany, M. (2025).
The effect of endurance training on weight changes, serum glucose levels, and NLRP-
1 protein expression in the hippocampus of male rats with diabetes, *Journal of New
Approaches in Exercise Physiology*, 7(13), 45-63.
DOI: 10.22054/nass.2025.89873.1195

Abstract

Purpose: Type 2 diabetes is a chronic metabolic disorder that, in addition to causing metabolic disturbances, has detrimental effects on the central nervous system, particularly the hippocampus. This study aimed to investigate the effects of endurance training on body weight changes, serum glucose levels, and NLRP-1 protein expression in the hippocampus of diabetic rats. **Method:** In this experimental study, 28 male Wistar rats, aged 10 weeks and weighing 245 grams, were divided into four groups: diabetic control, diabetic exercise, healthy control, and healthy exercise. Diabetes was induced by intraperitoneal injection of streptozotocin (STZ). The exercise groups underwent 6 weeks of endurance training on a treadmill, 5 sessions per week. Serum glucose levels, body weight, and NLRP-1 protein expression in the hippocampus were measured using standard techniques.

Results: The results showed that endurance training significantly reduced serum glucose levels and stabilized body weight in the diabetic exercise group compared to the diabetic control group ($p < 0.05$). Furthermore, NLRP-1 protein expression in the hippocampus was significantly decreased in the diabetic exercise group compared to the diabetic control group ($p < 0.05$). **Conclusion:** These findings indicate that endurance training positively impacts glucose metabolism and reduces neuroinflammation in a diabetic rat model. The decrease in NLRP-1 expression in the hippocampus suggests that endurance exercise has anti-inflammatory and neuroprotective effects. Endurance training, as a non-pharmacological strategy, could improve the management of diabetes and prevent neural damage in diabetic individuals.

Keywords: Endurance Training, Serum Glucose, NLRP-1 protein, Hippocampus, Diabetes.

Introduction

Diabetes mellitus (DM) is a common chronic metabolic disease defined by long-standing hyperglycemia due to impaired insulin secretion, impaired insulin action, or both. Persistent elevation of blood glucose not only drives classic microvascular and macrovascular complications but also affects the central nervous system (CNS), where it is increasingly recognized as a risk factor for cognitive decline and dementia in both type 1 and type 2 diabetes (Abdul Basith Khan et al., 2020). The hippocampus, a key region for learning, memory, and synaptic plasticity, appears particularly susceptible to metabolic and vascular insults, with diabetes associated with reduced hippocampal neurogenesis, structural atrophy, and deficits in multiple cognitive domains (Demir et al., 2021). Chronic hyperglycemia triggers a constellation of pathophysiological events including excess production of reactive oxygen species (ROS), mitochondrial dysfunction, endothelial injury, and disruption of blood–brain barrier integrity (Daryabor et al., 2020). These processes favor activation of inflammatory cascades and programmed cell death in neurons (Barone et al., 2021). Among the inflammatory mechanisms implicated in diabetes-related neurodegeneration, increasing attention has focused on inflammasomes, intracellular multiprotein complexes that control the maturation of interleukin (IL)-1 β and IL-18 and thereby orchestrate innate immune responses in the brain (Alizadeh et al., 2016). The NOD-like receptor family pyrin domain-containing 1 (NLRP-1) inflammasome is highly expressed in neurons and has been linked to neuronal injury under conditions of metabolic and oxidative stress (Zhou et al., 2019). Experimental reports in diabetic rodents demonstrate that NLRP1 signaling is upregulated in the hippocampus of diabetic rats, accompanied by increased caspase-1 activation and neuroinflammatory changes that contribute to memory impairment and behavioral alterations (Fang et al., 2013). These findings suggest that inappropriate activation of the NLRP-1 inflammasome is a key mediator coupling hyperglycemia to hippocampal damage (Borges et al., 2017).

At the systemic level, experimental diabetes induced by streptozotocin (STZ) in rodents reproduces cardinal clinical features seen in humans, including marked fasting hyperglycemia and characteristic reductions in body weight (Daneshyar et al., 2014). This catabolic phenotype

reflects insulin deficiency, enhanced lipolysis, and protein breakdown, and is widely used to model the metabolic milieu of uncontrolled diabetes (Colberg et al., 2010). Studies in STZ-induced diabetic rats consistently report significantly higher serum glucose concentrations and lower body mass compared with non-diabetic controls, underscoring the appropriateness of this model for evaluating interventions on glycemic control and weight trajectories (Sigal et al., 2006). Given the limitations, cost, and potential adverse effects of pharmacotherapy, lifestyle-based strategies—particularly structured exercise—are strongly encouraged as adjunctive or preventive measures in DM (Zanuso et al., 2017). Consensus guidelines and meta-analyses indicate that regular aerobic or combined training improves glycemic control, lowers fasting and postprandial glucose, enhances insulin sensitivity, and contributes to weight management in people with diabetes (Pedersen, 2019). In rodent models, endurance-type treadmill training over several weeks has been shown to reduce fasting glucose and modulate body weight in diabetic animals relative to sedentary diabetic counterparts (Colberg et al., 2010). Importantly, the benefits of endurance training extend beyond systemic metabolism to the CNS. Aerobic exercise promotes hippocampal plasticity, increases neurogenesis, and dampens oxidative and inflammatory signaling in the brain (El Assar et al., 2022). Recent experimental work in STZ-induced diabetic rats has demonstrated that a period of endurance training can lower hippocampal Panx1 and NLRP-1 protein expression while simultaneously reducing hyperglycemia, suggesting that improved metabolic control is accompanied by attenuation of inflammasome-related neuroinflammation (Zalouli et al., 2023).

Nevertheless, the interplay between systemic adaptations (changes in body weight and serum glucose) and central molecular responses (NLRP-1 expression in the hippocampus) in the context of endurance training has not been fully characterized in the diabetic state. It remains unclear to what extent exercise-induced improvements in glycemia and weight status are directly linked to downregulation of NLRP-1 mediated inflammatory signaling, or whether additional exercise-specific mechanisms contribute independently to neuroprotection. On this basis, the present study was designed to examine the effect of an endurance training program on body-weight changes, serum glucose levels, and hippocampal NLRP-1 protein expression in male rats with experimental diabetes. By jointly assessing systemic metabolic

parameters and a key marker associated with inflammation in the hippocampus, this study aimed to investigate the effect of endurance training on weight changes, serum glucose levels, and NLRP-1 protein expression in the hippocampus of male rats with diabetes (Fang et al., 2013; El Assar et al., 2022).

Methods

Study Design

This study was conducted in a laboratory setting with experimental and control groups. Thirty-two male Wistar rats (weight 250-300 g) were randomly divided into four groups: healthy control group (HC), diabetic control group (DC), diabetic training group (DT), and diabetic training control group (T). Diabetes was induced in diabetic groups using intraperitoneal injection of streptozotocin (STZ). The DT and T training groups performed endurance training on a treadmill for 30-60 minutes at an intensity of 50-80% VO₂max for 8 weeks, five days a week. All samples were kept in a room in the animal shelter of the research center. The mice were kept in special cages in groups of three in an environment with an average temperature of 22±2°C and a light-dark cycle of 12:12 hours. All mice had free access to water and special mouse food. Since the transportation of animals causes stress and consequently leads to physiological changes in them (15), after their transfer to the research environment, the mice were first trained to run on a treadmill for 1 week at a speed of 5-8 m/min for 15-20 minutes. During the training period, the intensity and duration of the training gradually increased. The control groups did not do any physical activity. 48 hours after the last training session, all Blood and hippocampal tissue samples were taken from the mice. Serum glucose and NLRP-1 protein levels in the hippocampus were measured using enzyme-linked immunosorbent assay (ELISA) and Real-Time PCR. Data were analyzed using one-way analysis of variance and Tukey's test.

Induction of diabetes and Exercise protocol

After completing the familiarization protocol, after 12 hours of food deprivation, by intraperitoneal injection of STZ solution (Sigma, St. Louis, MO; 50 mg/Kg dissolved in fresh citrate buffer 0.5 mol/L, pH 4.5): diabetes was induced. Non-diabetic mice were also injected with a volume equivalent of citrate buffer. 48 hours after the injection, by making a small wound on the tail vein with a lancet, a drop of blood was placed on a glucometer strip and the strip was measured by a glucometer device (Glucotrend 2, Roche, Germany). Then, the mice whose blood sugar was higher than 300 mg/dL were considered as diabetic. To ensure that the blood sugar does not return at the end of the training program, the blood sugar of the mice was also measured. The endurance training used in this research consisted of 8 weeks, 5 sessions per week of running with an intensity equivalent to the speed of 22-25 m/min (equivalent to 50% -80% of vo₂ max) on a treadmill for rodents. The time and intensity of each training session is shown in the table 1..

Table 1: Fasting serum glucose levels, body weight, and NLRP-1 (mean \pm standard deviation) in groups at baseline

Group	Body Weight (g)	Blood Glucose Level (mg/dl)	NLRP-1 (mg/ml)
(D)	230.63 \pm 22.05	542.23 \pm 16.62	2.741 \pm 0.122
(DT)	207.14 \pm 15.54	345.32 \pm 14.87	1.244 \pm 0.156
(C)	199.42 \pm 16.72	154.54 \pm 26.41	1.003 \pm 0.245
(T)	205.65 \pm 14.32	162.14 \pm 16.46	1.043 \pm 0.145

Results

The results of this study showed that endurance exercise significantly affected changes in body weight, serum glucose levels, and NLRP-1 protein expression in the hippocampal tissue of male diabetic rats. After 6 weeks of endurance exercise, the trained diabetic (DT) groups had a significant weight loss compared to the control diabetic (D) groups ($P < 0.05$). Also, serum glucose levels in the trained diabetic group decreased significantly ($P < 0.001$), while glucose levels remained high in the control diabetic group. Regarding the NLRP-1 protein, the results showed that the expression of this protein was significantly higher in the control diabetic group compared to the healthy groups. However, endurance training significantly reduced NLRP-1 protein levels in the trained diabetic group ($P < 0.001$), such that protein levels in these groups were significantly closer to those in the healthy control group. These findings suggest that endurance training not only improves glucose control in diabetic mice, but also modulates the negative effects of diabetes on the nervous system by reducing the expression of inflammatory proteins in the hippocampus.

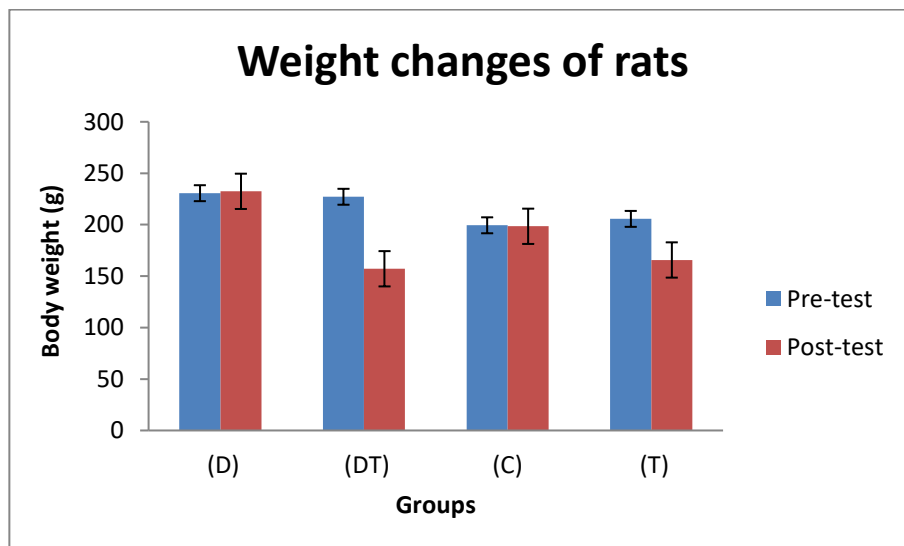


Figure 1: body weight (Mean±SEM) in groups C: control; D: diabetes control; DT: diabetes Training; T: Training

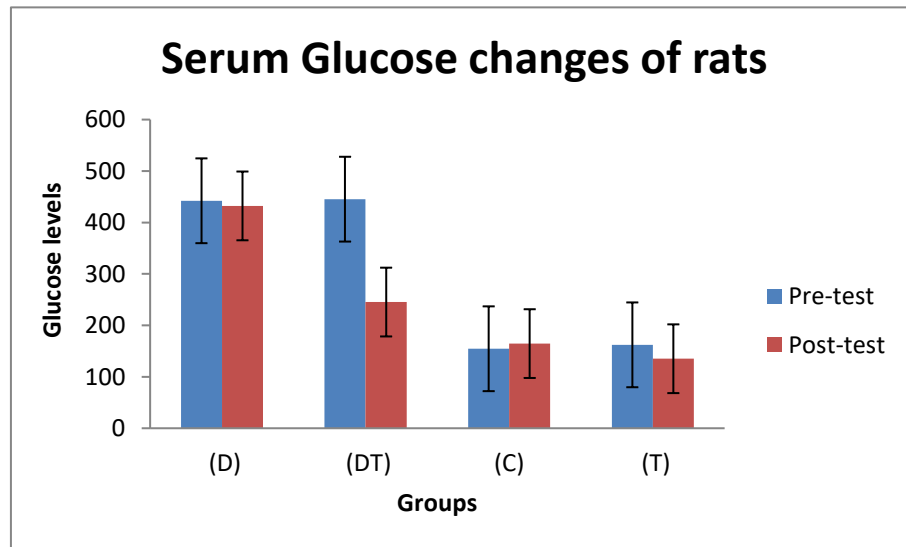


Figure 2: serum glucose levels (Mean±SEM) in groups C: control; D: diabetes control; DT: diabetes Training; T: Training

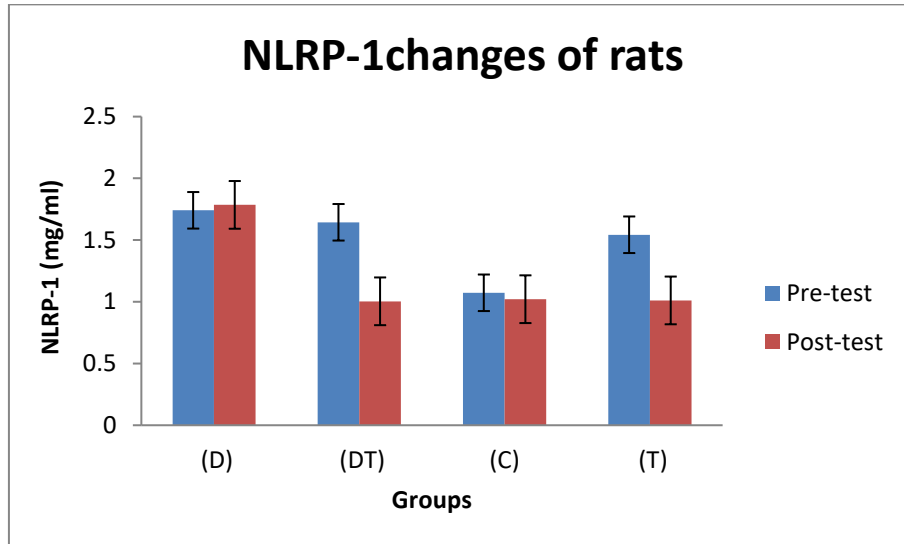


Figure 3: NLRP-1 protein levels in the hippocampus (Mean±SEM) in groups C: control; D: diabetes control; DT: diabetes Training; T: Training

The graphs above show the changes observed in body weight, blood glucose levels, and NLRP-1 protein expression in different groups before and after the endurance training period. Blue indicates pre-test values and red indicates post-test values.

Discussion

This study examined the impact of endurance training on weight changes, serum glucose levels, and NLRP-1 protein expression in the hippocampus of diabetic rats. Our results showed that endurance training reduced serum glucose and NLRP-1 protein levels and increased body weight.

One of the novel aspects of this study was the investigation of NLRP-1, a key inflammasome protein, in the hippocampus of diabetic rats. We observed that diabetes significantly elevated NLRP-1 expression in the hippocampal tissue, indicating increased neuroinflammation and potential neuronal damage. These findings are in line with the results of previous studies that have demonstrated the activation of the NLRP-1 inflammasome in response to chronic hyperglycemia (Fang et al., 2013). Elevated levels of NLRP-1 are associated with the activation of pro-inflammatory cytokines, such as IL-1 β , which are known to contribute to neuronal injury and cognitive decline (Zhou et al., 2019). In diabetic conditions, the persistent inflammatory response exacerbates neuronal damage in regions such as the hippocampus, which is critical for memory and learning processes (Ortiz et al., 2022).

Importantly, our results show that endurance training effectively reduced NLRP-1 expression in the hippocampus of diabetic rats, suggesting that exercise may alleviate neuroinflammation associated with diabetes. This finding is consistent with previous research indicating that exercise can reduce oxidative stress, enhance cerebral blood flow, and attenuate inflammatory responses in the brain (El Assar et al., 2022). Exercise-induced reductions in NLRP-1 expression likely reflect the anti-inflammatory and neuroprotective effects of endurance training. For instance, studies have shown that physical activity reduces levels of systemic inflammatory cytokines such as IL-6 and TNF- α , which are implicated in the activation of inflammasomes like NLRP-1 (Pedersen, 2019). Moreover, regular physical activity has been shown to promote neuroplasticity and reduce neuronal apoptosis, thus improving overall cognitive function (Zalouli et al., 2023).

Consistent with the well-documented effects of diabetes, our study found significant weight loss and elevated glucose levels in the diabetic control group. These findings align with previous research showing that diabetes, particularly when induced by streptozotocin (STZ), leads to hyperglycemia and subsequent loss of body mass (Fang et al., 2013).

Notably, endurance training mitigated these effects by stabilizing body weight and significantly reducing serum glucose levels in the diabetic exercise group (DT). This finding echoes previous studies that have demonstrated the benefits of endurance exercise in regulating glucose metabolism, improving insulin sensitivity, and preventing further weight loss in diabetic animals (Mohammadi et al., 2023; Daneshyar et al., 2014). The weight reduction observed in the control diabetic group can be attributed to the negative metabolic effects of prolonged hyperglycemia, which often leads to muscle catabolism and reduced fat storage (Barcelos et al., 2020). However, the exercise group, by improving glucose homeostasis, was able to prevent this muscle loss and maintain a more stable body weight (Sigal et al., 2006).

The positive impact of endurance training on glucose metabolism can also be explained by the modulation of insulin signaling and glucose uptake in skeletal muscle and adipose tissue. Research by Colberg et al. (2010) and Zanuso et al. (2017) supports our findings, showing that aerobic exercise enhances peripheral glucose utilization, reduces hepatic glucose production, and improves insulin sensitivity in diabetic individuals. Therefore, the reduction in glucose levels and the maintenance of body weight in the endurance-trained rats may be due to improved metabolic control, which helps counteract the hyperglycemic environment in the body. The present study provides compelling evidence of the interrelationship between metabolic dysfunction (weight and glucose) and neuroinflammation (NLRP-1) in diabetic rats. Our findings suggest that endurance training not only improves glucose control and stabilizes body weight but also reduces neuroinflammation, particularly in the hippocampus. The correlation observed between serum glucose levels and NLRP-1 expression in the diabetic rats supports the idea that hyperglycemia is a driving force behind the activation of inflammasomes in the brain. This is consistent with the results of Candeias et al. (2018), who demonstrated a strong correlation between blood glucose levels and the expression of neuroinflammatory markers in diabetic patients. Furthermore, our study

highlights the potential of endurance training to concurrently regulate metabolic and inflammatory processes, which could offer a multifaceted approach to managing diabetes-induced cognitive and neurological complications. However, further research is needed to explore the underlying molecular mechanisms by which exercise influences inflammasome activation and neuronal protection. Additionally, investigating the effects of different exercise intensities, durations, and modalities on NLRP-1 and other inflammatory markers will help optimize exercise protocols for individuals with diabetes and provide further insight into the neuroprotective benefits of physical activity.

Conclusion

These findings support the therapeutic role of physical activity as a non-pharmacological intervention to prevent or alleviate the metabolic and neurological complications of diabetes. Further research is needed to explore the molecular mechanisms underlying these effects and to optimize exercise protocols for diabetic individuals.

Funding:

This research received no external funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Acknowledgments:

We are grateful to all those who helped us in conducting this research.

Conflicts of Interest:

The author declares no conflict of interest.

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How to Cite: Ahadiyan, M; Karimjuzani, M. & Ahmadpour Torkamany, M. (2025). The effect of endurance training on weight changes, serum glucose levels, and NLRP-1 protein expression in the hippocampus of male rats with diabetes, *Journal of New Approaches in Exercise Physiology*, 7(13), 45-63 .

DOI: 10.22054/nass.2025.89873.1195



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