Diabetology & Metabolic Syndrome

RESEARCH

Open Access

Effects of aerobic and anaerobic exercise on glucose, lipid, and inflammation-related gene expression in the brain tissue of streptozotocin-induced diabetic rat model

Yakup Kılıç[1†], Semih Dalkılıç[2†], Lütfiye Kadıoğlu Dalkılıç[2†], Emrah Özdemir[3†], Fatih Mehmet Uğurlu[1†], Ragıp Pala[1†], Yeliz Ayyıldız[4†], Sezgin Hepsert[1*†] and Ercan Ayılgan[5†]

Abstract

Background Type 2 diabetes mellitus (T2DM) is a common metabolic disease characterized by elevated blood glucose levels accompanied by inadequate insulin secretion. In this study, we aimed to determine the expression levels of PEPCK, FAS, INSIG-1 and TNF-α genes, which play a key role in metabolism and inflammation processes, in brain tissue of rats with streptozotocin (STZ)-induced diabetes and to investigate how these gene expressions are affected by different exercise protocols.

Methods In this study, 40 male Wistar albino rats were randomly divided into four groups: Control group (C), Diabetes Sedentary group (DS), Diabetes Heavy Exercise group (DHE) and Diabetes Light Exercise group (DLE). Diabetes was induced by a single dose of intraperitoneally administered streptozotocin (STZ, 60 mg/kg). After diabetes induction, rats were subjected to treadmill exercise 5 days a week for 6 weeks. 24 h after the last exercise session, rats were sacrificed by decapitation and brain tissues were sent to the laboratory for molecular analysis.

Results A significant decrease in FAS ($p=0.002$) and TNF-α ($p=0.044$) levels was observed in the DHE group, while a significant increase in PEPCK ($p=0.009$) and INSIG1 ($p=0.019$) levels and a significant decrease in FAS ($p=0.037$) and TNF-α ($p=0.014$) levels were found in the DLE group. In addition, blood glucose levels were significantly decreased in the exercise groups compared to the diabetic sedentary group ($p=0.001$).

Conclusion This study revealed that exercise protocols of different intensities induce significant changes in the expression levels of some metabolic and inflammatory genes in brain tissue and decrease blood glucose levels in rats

†Yakup Kılıç and Semih Dalkılıç contributed equally to this work.

†Lütfiye Dalkılıç, Emrah Özdemir, Fatih Mehmet Uğurlu, Ragıp Pala, Yeliz Ayyıldız, Sezgin Hepsert and Ercan Ayılgan also contributed equally to this work.

*Correspondence:
Sezgin Hepsert
211301208@firat.edu.tr

Full list of author information is available at the end of the article

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

with streptozotocin-induced diabetes model. The findings suggest that exercise may partially modulate the molecular processes in the central nervous system of diabetes and may offer potential therapeutic contributions.

Keywords Diabetes, Exercise, Brain tissue, Gene expression

Introduction

T2DM is characterized by chronic hyperglycemia, dyslipidemia, arterial hypertension, and endothelial dysfunction [1]. In 2019, it affected 9.3% of the adult population globally, while this rate is projected to increase to 10.2% in 2030 [2]. The disease involves a combination of genetic, metabolic, and environmental factors that interact with each other. In this context, ethnicity, family history, and genetic predisposition constitute non-modifiable risk factors for T2DM, while obesity, sedentary lifestyle, and unhealthy diet constitute modifiable risks [3]. Although uniform exercise protocols are more frequently preferred in determining the pathology of T2DM disease, it has been suggested that multiple exercise approaches produce more effective results in patients [4]. The treatment of T2DM [5], which occurs with impaired carbohydrate, lipid, and protein metabolism, is managed with anti-diabetic drugs [6], pharmacologic drugs [7], and exercise [8]. At this point, exercise interventions are a cornerstone as they improve endothelial function and blood lipid profiles as well as glycemic control in patients [9]. Exercise therapy is a fundamental approach in the management of T2DM, providing multifaceted benefits such as improving glycemic control, increasing insulin sensitivity and reducing cardiovascular risks [10]. However, aerobic and anaerobic forms of exercise differ in their effects on metabolic pathways and pathophysiology. Aerobic exercise promotes glucose uptake and energy expenditure by increasing the activation of oxidative metabolism, whereas anaerobic exercise induces adaptations such as improvements in muscle mass and insulin sensitivity through high-intensity, short-term muscle contractions [11]. Therefore, a detailed study of the molecular and physiological effects of different exercise modalities in diabetic models is important for mechanistic understanding of the disease and optimizing treatment strategies [12].

T2DM is one of the most damaging and common endocrine diseases affecting glucose and lipid metabolism. Altered genes in pathways such as glucose and lipid metabolism, the insulin signaling pathway, and the adipocytokine signaling pathway are effective in the development of this disease [13]. Therefore, many studies have been conducted on genes that affect T2DM [14–16]. When examined individually, it is seen that genes such as TNF-α (Tumor Necrosis Factor Alpha), FAS (Fatty Acid Synthase), INSIG1 (Insulin Induced Gene 1) and PEPCK (Phosphoenolpyruvate Carboxykinase) are regulated differently in diabetic brain tissue and the increase or decrease in the secretion of these genes plays an active role in T2DM [17–20].

TNF-α, characterized as an adipocyte, is closely associated with glucose regulation and cardiovascular function [21]. TNF-α is an effective proinflammatory cytokine that induces insulin resistance in this disease [22]. INSIG1 gene expression has a regulatory effect on lipid metabolism. Increased expression prevents the existing disorder, while decreased expression is characterized by an imbalance in metabolism [23, 24]. PEPCK isoforms are regulated and activated by different physiological and pathological stimuli such as corticoids, hormones, starvation, and hypoxia. However, the effect of this isoform on glucose homeostasis has not been clarified [25]. FAS affects cell membrane permeability and the translocation of glucose transporters. In this context, it can be suggested that it has an important role in the development of insulin resistance and T2DM. In addition, specific FAS combinations in phospholipids and triglycerides are strongly associated with T2DM risk [26].

Pancreas (β-cells and α-cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue are among the organs involved in the development of T2DM [27]. In this study, we aimed to investigate the effects of different types of exercise protocols on PEPCK, INSIG1, FAS, and TNF-α gene expression levels in brain tissue of STZ-induced diabetes-induced rats and to determine their potential ameliorative role for T2DM.

Method

Study design

A randomized controlled experimental design was used in this study. The sample size was determined using G*Power 3.1.9.7 (Franz Faul, Universität Kiel, Germany). Accordingly, using type I error (alpha) 0.05, power (1-beta) 0.85 and effect size 0.60, it was determined that the minimum sample size should be at least 10 for each group (total 40) for a significant difference to occur. The rats used in the study were Sprague-Dawley rats, 8 weeks old and male. The rats were housed in plastic cages with wire lids, with a room temperature of 22 ± 2 °C, relative humidity of 35–40%, cage light intensity of 40 lx, and noise level below 85 dB, and water and feed were given ad libitum. As inclusion criteria, male Wistar albino rats with healthy physiological characteristics, 8–10 weeks of age and weighing 200–250 g were included in the study. Exclusion criteria included the development of disease, excessive weight loss, movement restriction, behavioral abnormalities, post-injection complications and failure

Table 1 Random assignment of rats to groups

Subject	1	2	3	4	5	6	7	8	9	10
Groups	DHE	DS	DS	DLE	DHE	DHE	DS	C	C	C
Subject	11	12	13	14	15	16	17	18	19	20
Groups	DHE	DS	DS	C	DLE	C	DS	DS	DS	C
Subject	21	22	23	24	25	26	27	28	29	30
Groups	DLE	DLE	DS	DHE	DLE	DHE	DLE	DLE	DLE	DHE
Subject	31	32	33	34	35	36	37	38	39	40
Groups	C	DS	DHE	C	DHE	DHE	DLE	C	DLE	C

Control, DS; Diabetes Sedentary, DHE; Diabetes Heavy Exercise, DLE; Diabetes Light Exercise

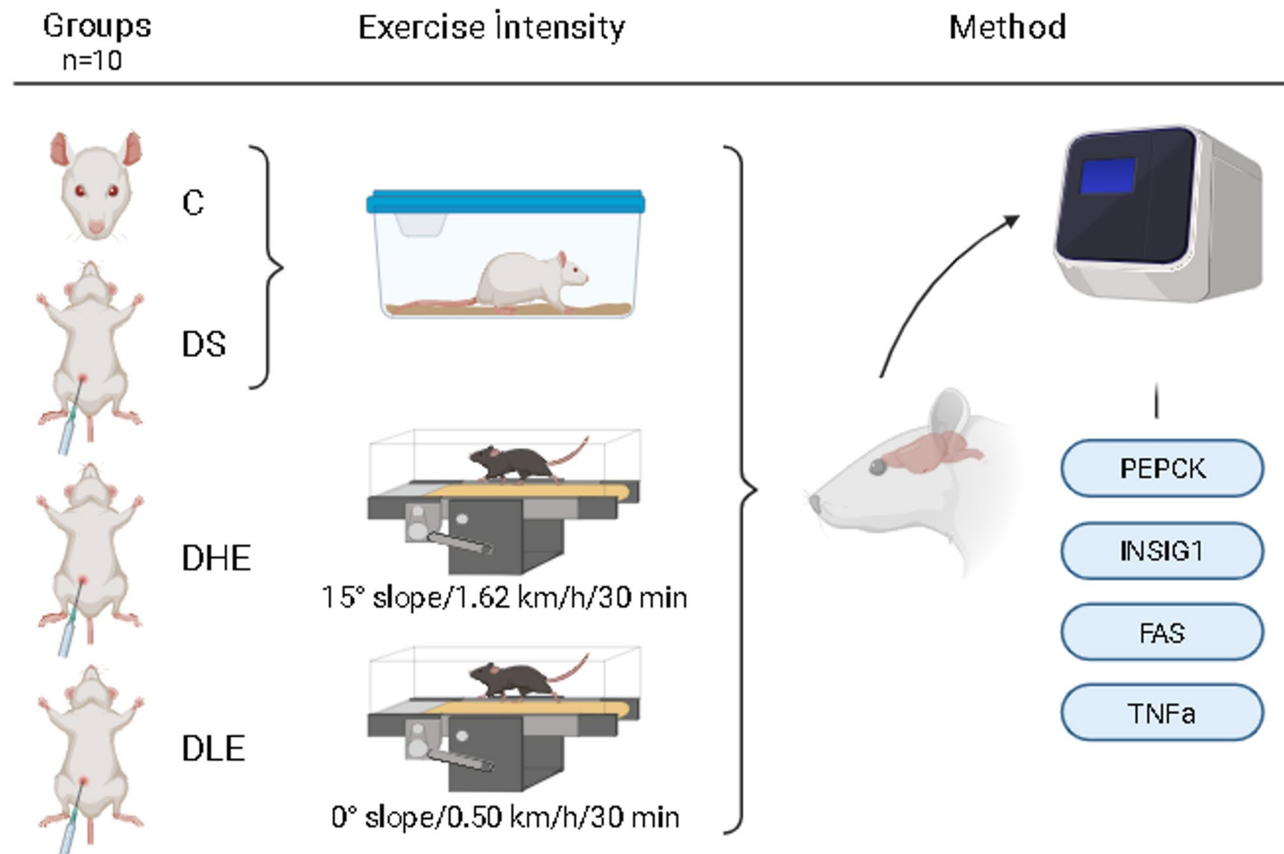

Fig. 1 Experimental Design. Control, DS; Diabetes Sedentary, DHE; Diabetes Heavy Exercise, DLE; Diabetes Light Exercise

to comply with exercise protocols during the experimental period. The rats were randomly divided into 4 groups as Control (C), Diabetes sedentary (DS), Diabetes Heavy Exercise (DHE) and Diabetes Light Exercise (DLE) (Table 1). In group C, diabetes was not induced and no exercise was performed. In the DS group, diabetes was induced and no exercise was performed. In the DHE group, diabetes was induced and heavy exercise was applied. In the DLE group, diabetes was induced and light exercise was applied (Fig. 1). While diabetes was induced in rats, the STZ dose was 60 mg/kg, dissolved in 0.1 molar citrate buffer with a pH of 4.5 and administered intraperitoneally [28]. STZ was administered 1 time, and the frequency of administration was set as a single injection. A blood glucose level of more than 200 mg/dL determined from the tail vein was set as the threshold value for diabetic assumption [28]. After 72 h, diabetes was confirmed. Blood glucose level, length, and body weight of the rats were measured at the 1st and 6th weeks of the study (Table 2). At the end of the 6th week, the rats were decapitated and the expression of PEPCK, INSIG1, FAS, and TNFα was analyzed in brain tissues. Rats were euthanized under deep anesthesia. A combination of ketamine (90 mg/kg) and xylazine (10 mg/kg) was administered intraperitoneally for anesthesia. After deep anesthesia was achieved, the mice were euthanized by cervical dislocation when reflexes disappeared and consciousness was completely lost [29]. In addition, the study

Table 2 Descriptive statistics of rats

		C (*n* = 10)	DS (*n* = 10)	DHE (*n* = 10)	DLE (*n* = 10)
Body Weight (g)	**Pre**	196.9 ± 8.40	226.3 ± 11.4	238.1 ± 8.3	241.2 ± 6.6
	Post	250.7 ± 6.3[c]	207.6 ± 9.3[bc]	216.7 ± 6.1[b]	219.8 ± 7.2[a]
Body Height (cm)	**Pre**	19.2 ± 0.6	19.4 ± 0.3	20.1 ± 0.7	20.7 ± 0.6
	Post	20.9 ± 0.4[a]	21.2 ± 0.5[b]	21.5 ± 0.5[c]	22.2 ± 0.9[c]
Blood Glucose (mg/dl)	**Pre**	101.5 ± 9.4	267.9 ± 17.3	328.6 ± 19.2	311.7 ± 22.7
	Post	139.8 ± 18.9[a]	390.3 ± 23.6[b]	239.1 ± 21.7[c]	209.3 ± 17.1[d]

Control, DS; Diabetes Sedentary, DHE; Diabetes Heavy Exercise, DLE; Diabetes Light Exercise. Different letters symbolize meaningful differences between themselves

was conducted according to the guidelines of the Declaration of Helsinki and approved by Fırat University Animal Experiments and Local Ethics Committee (2020/10).

According to Table 1, it is seen that the rats were assigned to the groups randomly and in equal numbers.

Exercise training

Treadmill exercise (MAY-TME 0804, Commat Limited) was performed between 08:00 and 10:00 am every day, 5 days a week for 6 weeks. The aerobic exercise protocol was applied to rats in the DLE group, which were exercised for 30 min per day at 0° incline and 0.50 km/h in a low-intensity exercise pattern. The anaerobic exercise protocol was applied to the DHE group and rats in this group were subjected to higher intensity treadmill exercise at 15° incline and 1.62 km/h for 30 min. These exercise protocols were based on established patterns of exercise intensity in rats. In the literature, it has been reported that exercises performed at 0° incline and 0.50 km/h speed range correspond to approximately 45–60% VO_2max and activate aerobic metabolism. On the other hand, protocols performed at 15° inclination and speeds above 1.60 km/h reach 80–100% VO_2max levels, activating anaerobic energy systems and generating physiological responses characterized by muscle fatigue and lactate accumulation [30–33].

Collection of tissues

The rats were sacrificed under appropriate conditions, and brain tissues were transferred into RNA Later solution for preservation of RNA. After incubating the solution for one day at 4 °C, the excess RNA Later solution was discarded. Within two weeks, total RNA was isolated from the tissue samples, which were kept at -20 °C [29].

RNA isolation from tissue samples

The RNA isolation from the samples was performed utilizing the Invitrogen PureLink Total RNA Kit, recommended protocol by the manufacturer was manipulated. Briefly, Tissue samples of 100 mg that were crushed on ice were placed into 2-mL Eppendorf tubes. Each tube with samples was added 1000 mL of Trizol and 5 µL of DTT, and they were homogenized by being vortexed for 5 min with one measure of zirconium beads added. Afterwards, the samples were incubated on ice for 15 min by being vortexed at 5-minute intervals. Following the incubation, the samples were centrifuged at 14,000 rpm for 10 min at 4C°. The supernatants were transposed to other Eppendorf tubes to which 200 µl of chloroform was added each, and the tubes were vortexed until their colours changed. Following another 10-minute incubation on ice, liquids consisting of three phases were obtained (DNA in the lower phase, protein in the middle section, and RNA in the upper phase). With each sample, the RNA part was transferred to another Eppendorf tube, and it was diluted with isopropyl alcohol at a 1:1 volume ratio. After the solution was vortexed for 3–5 min, it was incubated on ice for 10 min. The sample was centrifuged for 15 min at 14,000 rpm at 4C°. Subsequently, the whole supernatant was removed from the pellet, to which 1 ml of 75% ethyl alcohol was added, and they were vortexed. The final 5-minute centrifugation was made at 14,000 rpm. The precipitating pellet obtained was removed and incubated on ice for 6 min with the lids open. Diethylpyrocarbonate (DEPC) was added according to the amount of RNA solution. The RNA sample solution was kept on ice for 15–20 min [34].

Quality and control of RNAs

Gels with 1% agarose and 5 µl of Red Safe stain were used to run the isolated RNA samples for 20–30 min. The RNA 18 S 28 S bands were projected on the Invitrogen IBright 750 UV gel imaging system to examine the degradation of RNAs. The RNA samples that were found suitable were used for cDNA synthesis. Further, the concentrations of RNA samples were assessed in a Qubit Fluoro Meter instrument using Qubit HS RNA Assay Kit. Based on the results, an average value for concentrations was set, and from this initial concentration, cDNA synthesis was carried out. Complementary DNA was synthesized from suitable quality RNA samples using Applied Biosystems High-Capacity cDNA Reverse Transcription Kits (Lot: 01096160 REF: 4368814) with processes of 10 min at 25 °C, 120 min at 37 °C, 5 min at 85 °C, and 4 °C [35].

Quantitative Real-Time (qRT)-PCR

For the normalization of the mRNA gene, the GAPDH (glyceraldehyde 3-phosphate dehydrogenase) gene was

used as the control (housekeeping) gene during Real-Time PCR. The mRNA gene expression level was determined through a qRT-PCR reaction after the cDNA synthesis. The Applied Biosystem Step One Plus Real-Time instrument performed the PCR in the synthesized cDNA samples. The conditions for the qRT-PCR were one cycle at 95 °C for 3 min, 15 s at 95 °C, 10 s at 54 °C, and 15 s at 72 °C, and 40 at 95 °C for 20 s. The cycle was determined as 1 min at 60 °C and 15 s at 95 °C. The Relative Gene Expression algorithm was used to determine the expression level of each gene during qRT-PCR. Fold changes (Fc) were used to convey changes in gene expression [35].

Statistical analysis

The data obtained were analyzed in SPSS 22.0 (IBM, Armonk, NY, USA) package program. GraphPad Prism 8 was also used to prepare the figures. Since the sample size was less than 50, the Shapiro-Wilk test was applied to evaluate the normality assumption of the data sets. According to the p value obtained, it was decided that the data were suitable for parametric analysis ($p > 0.05$) [36]. ANCOVA test was used for post-test comparisons in descriptive statistics between groups of rats. A one-way ANOVA test was used for comparisons between groups. The homogeneity of group variances in the data set was checked by Levene's test and the variances were found to be homogeneous ($p > 0.05$). Therefore, LSD (Least Significant Difference) post hoc test, which is parametric and has high statistical power, was preferred for multiple comparisons between groups. In addition, the effect sizes of the ANOVA test results of the participants were determined according to the partial eta squared (η^2) result. Accordingly, small ($\eta^2 > 0.01$), medium ($\eta^2 > 0.06$), and large ($\eta^2 > 0.14$) effect sizes were interpreted [37]. The significance level was set as $p < 0.05$ in all tests.

Results

In Table 2, a significant difference was found according to the results of the analysis performed on the posttest measurements between the groups for height ($F = 112.761$; $p < 0.05$). According to the results of the analysis performed on the post-test measurements between the groups for the height of the groups, a significant difference was found ($F = 14.320$; $p < 0.05$). According to the results of the analysis performed on the post-test measurements between the groups for the blood glucose levels of the groups, a significant difference was determined ($F = 581.786$; $p < 0.05$).

According to the results of the analysis in Fig. 2, PEPCK mRNA level in brain tissue had the lowest value in the diabetes sedentary group, while the expression level of the gene was found to be upregulated as a result of heavy exercise and light exercise. A significant difference was

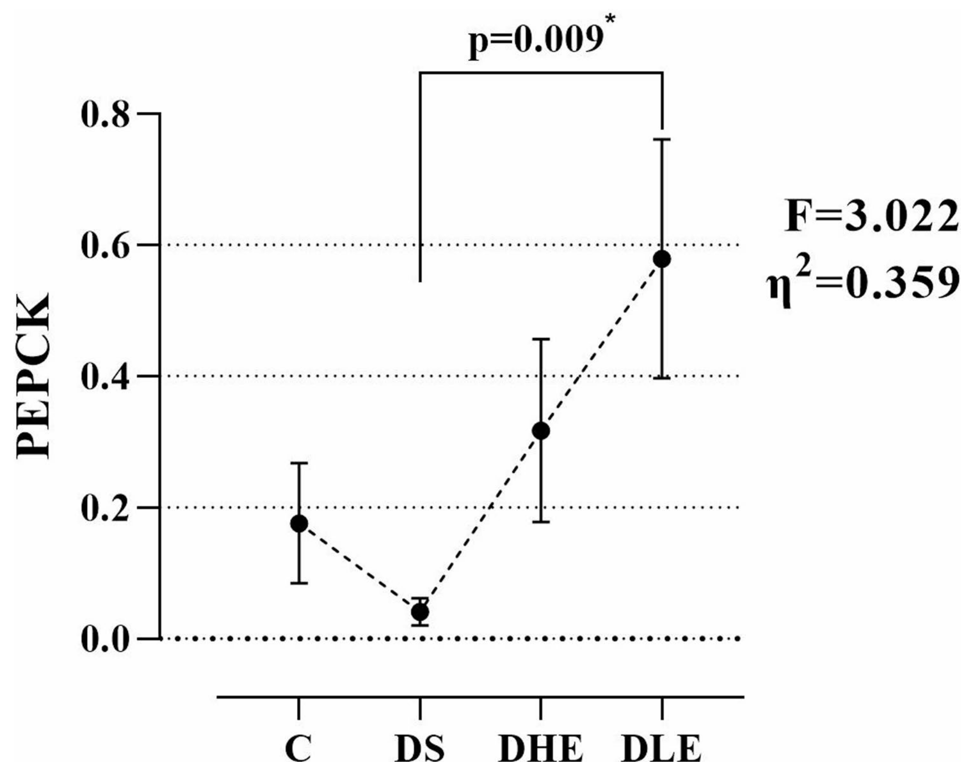

Fig. 2 PEPCK gene expression analysis results in four different groups. *;$p < 0.05$. C; Control, DS; Diabetes Sedentary, DHE; Diabetes Heavy Exercise, DLE; Diabetes Light Exercise

found between the diabetes mild exercise and sedentary diabetes groups ($p < 0.05$).

According to the results of the analysis in Fig. 3, INSIG1 mRNA level in brain tissue had the lowest value in the diabetes sedentary group, while the expression level of the gene was found to be upregulated as a result of heavy and light exercise. A significant difference was found between the diabetes mild exercise and diabetes sedentary groups ($p < 0.05$).

According to the results of the analysis in Fig. 4, the FAS mRNA level in the brain tissue was highest in the sedentary group, while the expression level of the gene was found to be downregulated as a result of heavy and light exercise. Significant differences were found between the diabetes heavy exercise and diabetes sedentary, the diabetes light exercise and diabetes sedentary groups ($p < 0.05$).

According to the results of the analysis in Fig. 5, TNF-α mRNA level in brain tissue was highest in the sedentary group, whereas the expression level of the gene was found to be downregulated as a result of heavy and light exercise. Significant differences were found between the diabetes heavy exercise and diabetes sedentary, the diabetes light exercise and diabetes sedentary groups ($p < 0.05$).

Discussion

According to this study, light and heavy exercise programs down-regulated FAS and TNF-α mRNA levels in the brain tissue of rats compared to the DS group, while INSIG1 and PEPCK mRNA levels were up-regulated. In addition, when the mean values are analyzed, it is seen that exercises of different intensities have different effects on the expression levels of the genes examined.

Exercise is one of the important treatment elements in T2DM disease, along with diet and medication [38]. When the literature is examined, it is seen that there are studies examining the effect of different exercise protocols on T2DM [39, 40]. However, due to the focus on light exercise [41], there is no consensus on the relative effects of different types of exercise. In addition, the limited number of studies on genes from brain tissue that play a key role in glucose and lipid metabolism is noteworthy.

In this study, PEPCK mRNA levels were found to be significantly increased after mild exercise in brain tissues of rats modeled for diabetes. PEPCK is a critical enzyme in gluconeogenesis and is highly expressed in classical metabolic tissues such as liver and kidney, while its presence and function in the brain has received increasing attention in recent years [42]. There are different findings in the literature regarding the effects of exercise on PEPCK expression. PEPCK plays an important role in the

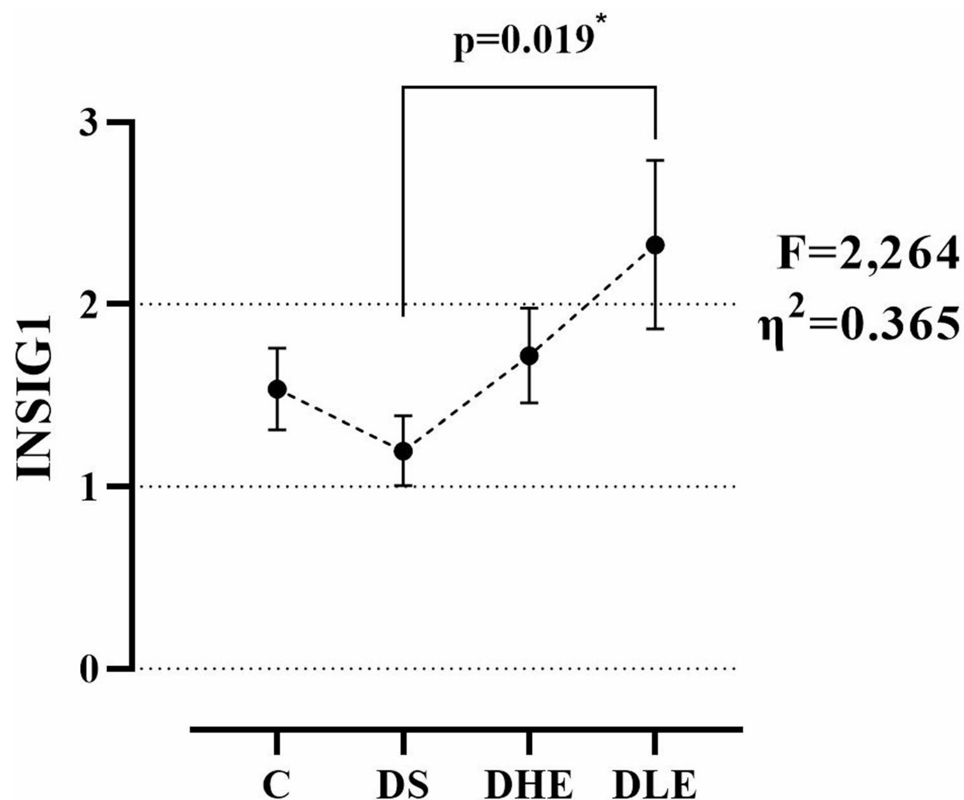

Fig. 3 INSIG1 gene expression analysis results in four different groups. *;$p < 0.05$. C; Control, DS; Diabetes Sedentary, DHE; Diabetes Heavy Exercise, DLE; Diabetes Light Exercise

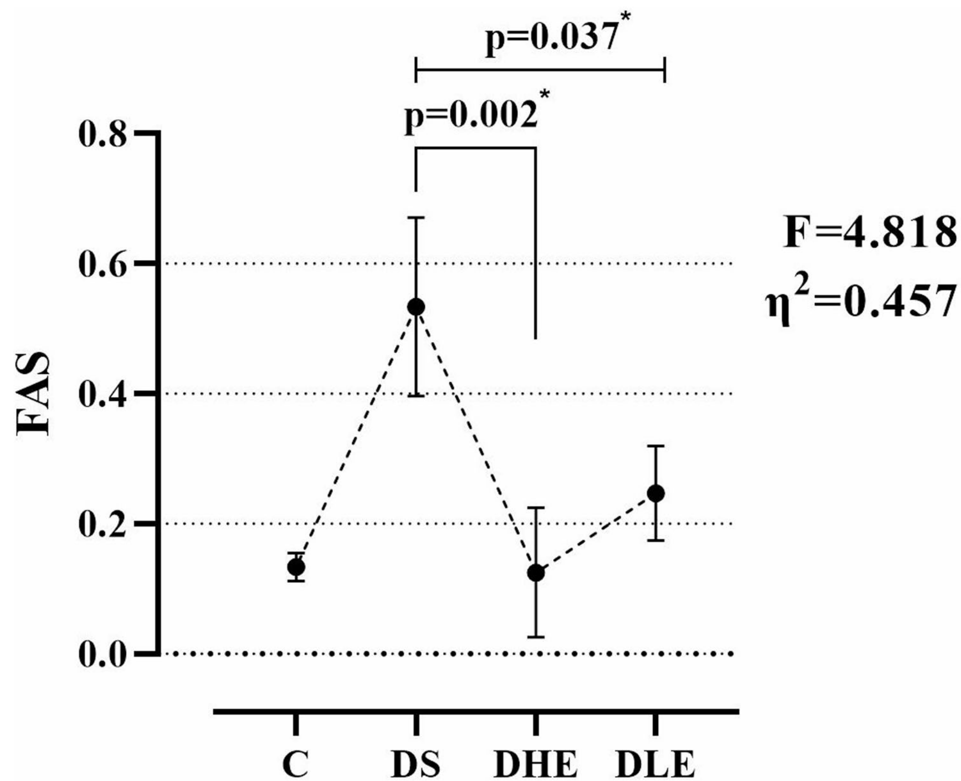

Fig. 4 FAS gene expression analysis results in four different groups. *;$p < 0.05$. C; Control, DS; Diabetes Sedentary, DHE; Diabetes Heavy Exercise, DLE; Diabetes Light Exercise

regulation of glycogenolysis and gluconeogenesis [43]. In a study, it was reported that acute responses of PEPCK mRNA levels changed in rats exposed to 60 min of moderate exercise. Accordingly, mRNA levels decreased 4 h after exercise and increased 10 h later compared to resting rats [44]. In our study, the chronic effect of PEPCK mRNA levels after different exercise treatments was examined and it was reported that mRNA levels increased as a result of both light and heavy exercise. A significant difference was found especially between DLE and DS groups. However, in a study by Li et al. (2023), it was shown that post-exercise conditioning applied after ischemic brain injury reduced ischemic damage by suppressing cerebral gluconeogenesis. In this study, it was reported that PEPCK1/2 expression decreased and this contributed to the suppression of gluconeogenesis [45]. This finding contrasts with the increase in PEPCK mRNA levels in our study and suggests that the effects of exercise may vary depending on factors such as tissue type, exercise intensity and duration. Furthermore, differences in pathological models (ischemia versus diabetes) may explain these discrepancies and highlight the complex regulation of PEPCK in the brain under different conditions.

In this study, FAS mRNA levels were found to be decreased after both light and heavy exercise in the brain tissues of diabetic model rats. The suppression of brain FAS expression by different intensities of exercise may have important implications for diabetic brain metabolism [46]. Decreased FAS mRNA levels suggest reduced fatty acid synthesis and altered metabolic adaptation processes in brain tissue. Previous studies emphasize that fatty acid metabolism is critical for neuronal functions and neuroprotection. However, it is not yet clear what kind of effects this reduction in FAS levels would have [47]. Given the diabetes-induced impairments in energy utilization in the rat brain, the suppression of FAS expression by exercise may be related to a reduced need for fatty acid synthesis. One potential mechanism underlying this effect is that AMP-activated protein kinase (AMPK) activated during exercise inhibits lipogenic enzymes such as FAS to promote energy homeostasis. Furthermore, exercise-induced suppression of the NF-κB signaling pathway may contribute to the reduction of neuroinflammation, which affects lipid metabolism and FAS expression [48–50]. However, a decrease in FAS levels may affect the synthesis of cellular membrane components and alter neurological function in the long term. There are a limited number of studies examining the effects of different exercises on FAS expression. Some studies reported that 6 weeks of moderate exercise reduced oxidative stress and apoptosis in diabetic rat brains [51]. In conclusion,

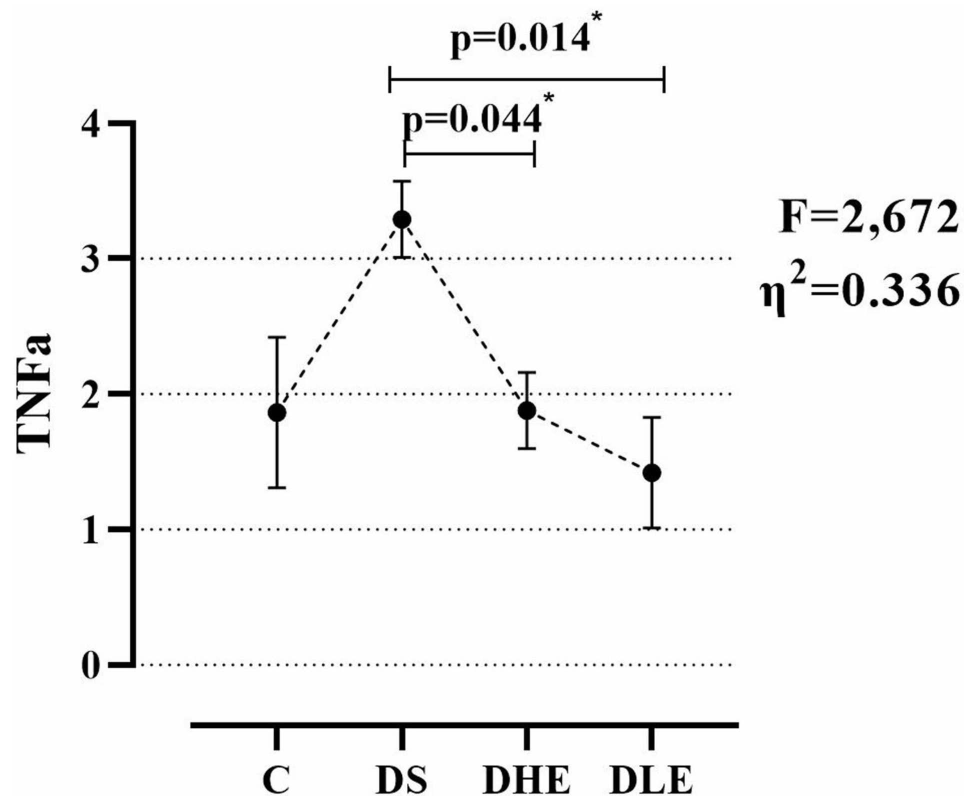

Fig. 5 TNFa gene expression analysis results in four different groups. *;$p < 0.05$. C; Control, DS; Diabetes Sedentary, DHE; Diabetes Heavy Exercise, DLE; Diabetes Light Exercise

more research is needed to determine the effects of different types of exercise on FAS mRNA expression. In particular, understanding the effects of exercise on brain lipid metabolism and FAS expression may be important in the management of neurological complications of diabetes.

Genome-wide association studies have been conducted to better define diabetes and in this direction, TNF-α is defined as one of the susceptible genes [52]. The − 308G > A polymorphism in the promoter region of the associated gene creates upregulation in its transcriptional activation [53], and obesity and insulin resistance are clinically linked to this variable [54]. There are conflicting results that TNF-α is positively affected by exercise. In fact, in one study, exercise decreased the level of leptin, which is associated with diabetes and lipid metabolism, but did not cause a significant difference in the expression level of the related gene [55]. In another study, it was reported that resistance exercise gave positive results with downregulation of this gene [56]. In a different study, it was reported that TNF-α expression decreased in the hippocampus of rats subjected to treadmill exercise for 4 weeks, and this may be attributed to the fact that exercise decreases neuroinflammation and causes an increase in synaptic protein expression [57]. Multiple mechanisms may be involved in exercise regulation of TNF-α expression, including AMP-activated protein kinase (AMPK) activation and suppression of the nuclear factor kappa B (NF-κB) signaling pathway, as well as reduction of oxidative stress, improvement of mitochondrial function, regulation of the hypothalamic-pituitary-adrenal (HPA) axis and exercise-induced release of myokines (e.g. interleukin-6). Together, these processes contribute to the reduction of neuroinflammation and maintenance of metabolic balance of brain tissue [58, 59]. In our study, we found that different types of exercise led to an improvement in TNF-α levels, suggesting a complex response to conflicting findings. Detailed analysis shows that heavy exercise is more effective on the basis of mean values.

INSIG-1 plays an important role in the regulation of lipid metabolism. According to the results of many studies, it is shown that the relevant gene has lower-than-normal values based on disorders in lipid metabolism. It is also thought that lipid disorders can be prevented by reaching high expression levels [60, 61]. When the literature studies were examined in detail, it was determined that the response of the gene to exercise therapy in diabetes was not sufficiently included. In a limited number of studies, it was found that resistance and endurance exercises positively affected the brain in rats with induced diabetes [62]. In addition, it has been stated that studies

involving exercise protocols of different intensities are needed to determine the optimum exercise intensity [63]. In our study, when the chronic results of the exercise protocols applied in response to this deficiency in rats were examined, it was concluded that there was an increase in mRNA levels and that the increase was more dominant in mild exercise, although it was significantly different from the average values. This increase in INSIG-1 expression may be driven by exercise-induced activation of sterol regulatory element-binding proteins (SREBPs) feedback pathways and upregulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which enhance mitochondrial biogenesis and lipid homeostasis. Furthermore, the anti-inflammatory and antioxidative effects of exercise may stabilize INSIG-1 mRNA, facilitating sustained expression in diabetic brain tissue. The more pronounced effect of mild exercise could be due to optimal cellular stress levels that favor adaptive gene regulation without inducing excessive metabolic strain [49, 64, 65].

Although this study was conducted with an experimental rat model, the regulatory effects of aerobic and anaerobic exercise on metabolic and inflammatory gene expressions in brain tissue provide meaningful clues for clinical translation to humans. In the context of neurological complications associated with type 2 diabetes, exercise-induced modulation of genes such as PEPCK, FAS, INSIG1 and TNF-α may contribute to the maintenance of metabolic homeostasis and reduction of neuroinflammation. These molecular adaptations may help delay diabetes-related cognitive impairments or neurodegenerative processes. Although clinical validation is required, these findings suggest that exercise-based interventions could be considered as a therapeutic strategy to reduce the central nervous system effects that accompany diabetes.

Limitations

The exercise interventions applied in this study were limited to a 6-week period only, and long-term effects were not assessed. Subject groups were not examined for levels of psychological stress potentially induced by the exercise protocols. Furthermore, insulin tolerance testing and glucose tolerance testing were not performed to further evaluate the metabolic effects of exercise on the development of T2DM. The study focused only on brain tissue and did not evaluate the expression levels of PEPCK, FAS, TNF-α and INSIG1 genes in other metabolically important peripheral tissues. Furthermore, the findings obtained at the mRNA level were not confirmed at the protein level, thus post-translational regulatory processes were ignored. In this context, further studies supported by protein level analyses such as Western blotting will contribute to a more holistic understanding of the biological relevance of the gene expression data obtained.

Future research should adopt a more comprehensive and multi-layered approach that includes not only transcriptome but also proteome analyses. It is also important to apply behavioral and cognitive tests to evaluate the functional correlates of molecular findings. Evaluating the effects of exercise on peripheral organs other than brain tissue, investigating gender differences, implementing long-term exercise programs and studies on the combination of exercise and pharmacological agents should be among the priority research topics in the future in order to expand the scope of therapeutic strategies in this field.

Conclusion

With reference to the DS group, significant impairments were observed in the mRNA levels of PEPCK, FAS, TNF-α and INSIG1 genes in diabetic rats. Regular heavy and light exercise protocols resulted in significant improvements in the expression levels of these genes compared to the DS group, but gene expressions did not reach the levels of the healthy C group. The fact that different exercise intensities did not cause significant changes in mRNA levels compared to the C group suggests that the effects of exercise on target genes may be more limited or complex, and more detailed studies are needed in this regard. In particular, DLE and DHE exercise protocols seem to lead to different results at the molecular level, suggesting mechanistic differences in the effects of exercise types on neurometabolic regulation. DLE was particularly more effective in increasing INSIG1 and PEPCK expressions, and this effect is thought to be associated with lower metabolic stress. On the other hand, DHE was more prominent in suppressing TNF-α expression, which may be related to anti-inflammatory pathways induced by exercise-induced lactate accumulation. These differences suggest that exercise intensity should be carefully selected to achieve targeted molecular effects in diabetes-related brain disorders. According to the findings, significant decreases were observed in FAS ($F = 4.818$; $p = 0.002$) and TNF-α ($F = 2.672$; $p = 0.044$) gene expressions in the DHE group compared to the DS group. Similarly, significant increases in PEPCK ($F = 3.022$; $p = 0.009$) and INSIG1 ($F = 2.264$; $p = 0.019$) gene expression and significant decreases in FAS ($F = 4.818$; $p = 0.037$) and TNF-α ($F = 2.672$; $p = 0.014$) gene expression were detected in the DLE group. These results suggest that exercise may lead to favorable changes in energy metabolism-related gene expressions in the diabetic brain. However, it should be taken into account that these effects do not provide a complete normalization, and more detailed studies should be conducted at the mechanistic level considering the contradictory findings in the literature.

This study provides a scientific basis for future research on the prevention of diabetes-related neurological complications by revealing the potential regulatory effects of exercise on neurometabolic processes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01893-4.

Supplementary Material 2

Author contributions

Y.K., S.D., L.D. contributed to the research concept and design, collection, and/or assembly of data, data analysis, and writing of the article. E.Ö., F.M.U contributed to data collection and assembly. R.P., Y.A. collected data, performed analysis and interpretation. S.H., E.A. drafted the manuscript. All authors reviewed the manuscript.

Funding

It was completed within the scope of the project numbered BSY. 20.02 of Fırat University Scientific Research Projects (FÜBAP).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was initiated after obtaining ethical approval by the decision of Fırat University Animal Experiments and Local Ethics Committee (2020/10).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Faculty of Sport Sciences, Firat University, Elazig, Turkey
[2]Faculty Of Science / Molecular Biology, Firat University, Elazig, Turkey
[3]Faculty of Sport Sciences, Rumeli University, Istanbul, Turkey
[4]Faculty of Sport Sciences, Alanya Alaaddin Keykubat University, Antalya, Turkey
[5]Republic of Türkiye Ministry of Youth and Sports, Ankara, Turkey

Received: 3 May 2025 / Accepted: 30 July 2025
Published online: 11 August 2025

References

1. Sociedade brasileira de diabetes. *Posicionamento Oficial SBD, SBPC-ML, SBEM e FENAD;2017/2018.*
2. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R, IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*. 2019;157:107843. https://doi.org/10.1016/j.diabres.2019.107843
3. Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med. 2013;159:543–51. https://doi.org/10.7326/0003-4819-159-8-201310150-00007.
4. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, Kirwan JP, Zierath JR. Exercise/Physical activity in individuals with type 2 diabetes: A consensus statement from the American college of sports medicine. Med Sci Sports Exerc. 2022;54(2):353–68. https://doi.org/10.1249/MSS.0000000000002800.
5. Artasensi A, Pedretti A, Vistoli G, Fumagalli L. Type 2 diabetes mellitus: A review of Multi-Target drugs. Molecules. 2020;25(8):1987. https://doi.org/10.3390/molecules25081987.
6. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care. 2020;43(2):487–93. https://doi.org/10.2337/dci19-0066.
7. McGovern A, Tippu Z, Hinton W, Munro N, Whyte M, de Lusignan S. Comparison of medication adherence and persistence in type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab. 2018;20(4):1040–3. https://doi.org/10.1111/dom.13160.
8. Sampath Kumar A, Maiya AG, Shastry BA, Vaishali K, Ravishankar N, Hazari A, Gundmi S, Jadhav R. Exercise and insulin resistance in type 2 diabetes mellitus: A systematic review and meta-analysis. Annals Phys Rehabilitation Med. 2019;62(2):98–103. https://doi.org/10.1016/j.rehab.2018.11.001.
9. Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. Indian J Endocrinol Metabol. 2015;19(1):160.
10. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, Horton ES, Castorino K, Tate DF. Physical activity/exercise and diabetes: a position statement of the American diabetes association. Diabetes Care. 2016;39(11):2065–79.
11. Gillen JB, Gibala MJ. Is high-intensity interval training a time-efficient exercise strategy to improve health and fitness? Appl Physiol Nutr Metab. 2014;39(3):409–12.
12. Mensberg P, Frandsen C, Carl CS, Espersen E, Leineweber T, Larsen EL, Storgaard H, Schlawitz K, Petersen THD, Poulsen JN, Sørensen F, Gørtz PM, Forman JL, Kiens B, Knop FK, Vilsbøll T. High-intensity interval training improves insulin sensitivity in individuals with prediabetes. Eur J Endocrinol. 2025;192(4):456–65.
13. Kaur P, Kotru S, Singh S, Behera BS, Munshi A. Role of MiRNAs in the pathogenesis of T2DM, insulin secretion, insulin resistance, and β cell dysfunction: the story so Far. J Physiol Biochem. 2020;76(4):485–502. https://doi.org/10.1007/s13105-020-00760-2.
14. Tang S, Liu W, Pan X, Liu L, Yang Y, Wang D, Xu P, Huang M, Chen Z. Specific Inhibition of plasminogen activator inhibitor 1 reduces blood glucose level by Lowering TNF-α. Life Sci. 2020;246:117404. https://doi.org/10.1016/j.lfs.2020.117404.
15. Zhu YX, Hu HQ, Zuo ML, Mao L, Song GL, Li TM, Dong LC, Yang ZB, Ali Sheikh MS. Effect of oxymatrine on liver gluconeogenesis is associated with the regulation of PEPCK and G6Pase expression and AKT phosphorylation. Biomedical Rep. 2021;15(1):56. https://doi.org/10.3892/br.2021.1432.
16. Xu LN, Yin LH, Jin Y, Qi Y, Han X, Xu YW, Liu KX, Zhao YY, Peng JY. Effect and possible mechanisms of Dioscin on ameliorating metabolic glycolipid metabolic disorder in type-2-diabetes. Phytomedicine. 2020;67:153139. https://doi.org/10.1016/j.phymed.2019.153139.
17. Gu L, Ding X, Wang Y, Gu M, Zhang J, Yan S, Li N, Song Z, Yin J, Lu L, Peng Y. Spexin alleviates insulin resistance and inhibits hepatic gluconeogenesis via the FoxO1/PGC-1α pathway in high-fat-diet-induced rats and insulin resistant cells. Int J Biol Sci. 2019;15(13):2815–29. https://doi.org/10.7150/ijbs.31781.
18. Lontchi-Yimagou E, Sobngwi E, Matsha TE, et al. Diabetes mellitus and inflammation. Curr Diab Rep. 2013;13:435–44. https://doi.org/10.1007/s11892-013-0375-y.
19. Hao JW, Wang J, Guo H, Zhao YY, Sun HH, Li YF, Lai XY, Zhao N, Wang X, Xie C, et al. CD36 facilitates fatty acid uptake by dynamic palmitoylation-regulated endocytosis. Nat Commun. 2020;11:4765. https://doi.org/10.1038/s41467-020-18565-8.
20. Zhao X, Liu Y, Liu J, Qin J. Therapeutic effects and mechanism of liraglutide in rats with type 2 diabetes and Metabolic-associated fatty liver disease. Endocr Metab Immune Disord Drug Targets. 2022;22(9):963–9. https://doi.org/10.2174/1871530322666220126151141.
21. Liu SX, Zheng F, Xie KL, Xie MR, Jiang LJ, Cai Y. Exercise reduces insulin resistance in type 2 diabetes mellitus via mediating the LncRNA MALAT1/MicroRNA-382-3p/Resistin axis. Mol Therapy Nucleic Acids. 2019;18:34–44. https://doi.org/10.1016/j.omtn.2019.08.002.
22. Nayak BS, Ramsingh D, Gooding S, Legall G, Bissram S, Mohammed A, Raychaudhuri A, Sahadeo B, Pandohie V, Figaro K. Plasma adiponectin levels are related to obesity, inflammation, blood lipids and insulin in type 2 diabetic and non-diabetic Trinidadians. Prim Care Diabetes. 2010;4(3):187–92. https://doi.org/10.1016/j.pcd.2010.05.006.

23. Dong XY, Tang SQ. Insulin-induced gene: a new regulator in lipid metabolism. Peptides. 2010;31(11):2145–50. https://doi.org/10.1016/j.peptides.2010.07.020.
24. Nguyen AD, Lee SH, DeBose-Boyd RA. Insig-mediated, sterol-accelerated degradation of the membrane domain of hamster 3-hydroxy-3-methylglutaryl-coenzyme A reductase in insect cells. J Biol Chem. 2009;284(39):26778–88. https://doi.org/10.1074/jbc.M109.032342.
25. Seenappa V, Joshi MB, Satyamoorthy K. Intricate regulation of phosphoenolpyruvate Carboxykinase (PEPCK) isoforms in normal physiology and disease. Curr Mol Med. 2019;19(4):247–72. https://doi.org/10.2174/1566524019666190404155801.
26. Shetty SS, Kumari S. Fatty acids and their role in type-2 diabetes (Review). Experimental Therapeutic Med. 2021;22(1):706. https://doi.org/10.3892/etm.2021.10138.
27. DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773–95.
28. Wang Z, Gleichmann H. GLUT2 in pancreatic islets: crucial target molecule in diabetes induced with multiple low doses of streptozotocin in mice. Diabetes. 1998;47(1):50–6.
29. National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals. Guide for the care and use of laboratory animals. 8th ed. Washington, DC: National Academies; 2011.
30. Qin F, Dong Y, Wang S, Xu M, Wang Z, Qu C, Yang Y, Zhao J. Maximum oxygen consumption and quantification of exercise intensity in untrained male Wistar rats. Sci Rep. 2020;10(1):11520.
31. Almeida JA, Petriz Bde A, da Costa Gomes CP, Pereira RW, Franco OL. Assessment of maximal lactate steady state during treadmill exercise in SHR. BMC Res Notes. 2012;5:661.
32. Lønbro S, Wiggins JM, Wittenborn T, Elming PB, Rice L, Pampo C, Lee JA, Siemann DW, Horsman MR. Reliability of blood lactate as a measure of exercise intensity in different strains of mice during forced treadmill running. PLoS ONE. 2019;14(5):e0215584.
33. Chavanelle V, Sirvent P, Ennequin G, Caillaud K, Montaurier C, Morio B, Boisseau N, Richard R. Comparison of oxygen consumption in rats during uphill (concentric) and downhill (eccentric) treadmill exercise tests. J Sports Sci Med. 2014;13(3):689–94.
34. Pan B, Ge L, Xun YQ, Chen YJ, Gao CY, Han X, Zuo LQ, Shan HQ, Yang KH, Ding GW, Tian JH. Exercise training modalities in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. Int J Behav Nutr Phys Activity. 2018;15(1):72. https://doi.org/10.1186/s12966-018-0703-3.
35. Özer H. Streptozotosin Ile Diyabet Oluşturulmuş Ratlarda Ağır Egzersizin ve Metformin Uygulamasının Kan Glukoz Düzeyi Ile Karaciğer ve Kas Dokusunda Cgrp (Kalsitonin gen Ilişkili peptit) ve Ldh (Laktatdehidrogenaz) gen Ifadesi Üzerine etkileri, [Yüksek Lisans Tezi]. Elazığ: Fırat Üniversitesi, Sağlık Bilimleri Enstitüsü; 2023.
36. Aldemir Ö. Diyabet Oluşturulmuş Ratlarda Egzersiz ve Metformin Uygulamasının Kas Dokusunda MCT1 ve MCT4, mRNA Seviyelerine etkisi, [Yüksek Lisans Tezi]. Elazığ: Fırat Üniversitesi, Sağlık Bilimleri Enstitüsü; 2023.
37. George D, Mallery. p. IBM SpSS statistics 26 step by step: A simple guide and reference. 16th ed. New York: Routledge; 2019.
38. Cohen J. Statistical power analysis for the behavioral sciences. Routledge; 2013. https://doi.org/10.4324/9780203771587.
39. Sigal RJ, Armstrong MJ, Colby P, et al. Canadian diabetes association 2013 clinical practice guidelines for the prevention and management of diabetes in canada: physical activity and diabetes. Can J Diabetes. 2013;37(suppl 1):S40–4.
40. Hou L, Wang Q, Pan B, Li R, Li Y, He J, Qin T, Cao L, Zhang N, Cao C, Ge L, Yang K. Exercise modalities for type 2 diabetes: A systematic review and network meta-analysis of randomized trials. Diabetes Metab Res Rev. 2023;39(1):e3591. https://doi.org/10.1002/dmrr.3591.
41. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. JAMA. 2001;286:1218–27.
42. Lu HH, Zhou Y, Chen C, Gu ZJ. Meta-analysis of the effect of exercise intervention on cognitive function in elderly patients with type 2 diabetes mellitus. BMC Geriatr. 2024;24(1):770. https://doi.org/10.1186/s12877-024-05352-z. PMID: 39300333; PMCID: PMC11411744.
43. Elnagar A, El-Dawy K, El-Belbasi HI, Rehan IF, Embark H, Al-Amgad Z, Shanab O, Mickdam E, Batiha GE, Alamery S, Fouad SS, Cavalu S, Youssef M. Ameliorative effect of Oxytocin on FBN1 and PEPCK gene expression, and behavioral patterns in rats' Obesity-Induced diabetes. Front Public Health. 2022;10:777129. https://doi.org/10.3389/fpubh.2022.777129.
44. Knudsen JG, Biensø RS, Hassing HA, Jakobsen AH, Pilegaard H. Exercise-induced regulation of key factors in substrate choice and gluconeogenesis in mouse liver. Mol Cell Biochem. 2015;403(1–2):209–17. https://doi.org/10.1007/s11010-015-2351-0.
45. Li J, Liu Y, Liu B, Li F, Hu J, Wang Q, Li M, Lou S. Mechanisms of aerobic exercise upregulating the expression of hippocampal synaptic Plasticity-Associated proteins in diabetic rats. Neural Plast. 2019;2019:7920540. https://doi.org/10.1155/2019/7920540. PMID: 30911292; PMCID: PMC6398012.
46. Pahlavani HA. Exercise-induced signaling pathways to counteracting cardiac apoptotic processes. Front Cell Dev Biol. 2022;10:950927. https://doi.org/10.3389/fcell.2022.950927.
47. Wang M, Xie K, Zhao S, Jia N, Zong Y, Gu W, Cai Y. Aerobic exercise improves cognitive impairment in mice with type 2 diabetes by regulating the MALAT1/miR-382-3p/BDNF signaling pathway in serum-exosomes. Mol Med. 2023;29(1):130. https://doi.org/10.1186/s10020-023-00727-1. PMID: 37740187; PMCID: PMC10517522.
48. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011;11(9):607–15.
49. Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. Nat Rev Mol Cell Biol. 2018;19(2):121–35.
50. Fan R, Kong J, Zhang J, Zhu L. Exercise as a therapeutic approach to alleviate diabetic kidney disease: mechanisms, clinical evidence and potential exercise prescriptions. Front Med (Lausanne). 2024;11:1471642. https://doi.org/10.3389/fmed.2024.1471642. PMID: 39526249; PMCID: PMC11543430.
51. Taheri A, Habibi A, Shakerian S, Tabandeh MR, Nikbakht M. Attenuation of apoptosis and oxidative stress by endurance training in the cerebellum of diabetic rats. Jentashapir J Cell Mol Biol. 2021;12(3).
52. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–7. https://doi.org/10.1038/nature05485.
53. Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proc Natl Acad Sci U S A. 1997;94(7):3195–9. https://doi.org/10.1073/pnas.94.7.3195.
54. Herrmann SM, Ricard S, Nicaud V, Mallet C, Arveiler D, Evans A, Ruidavets JB, Luc G, Bara L, Parra HJ, Poirier O, Cambien F. Polymorphisms of the tumour necrosis factor-alpha gene, coronary heart disease and obesity. Eur J Clin Invest. 1998;28(1):59–66. https://doi.org/10.1046/j.1365-2362.1998.00244.x.
55. Halle M, Berg A, Northoff H, Keul J. Importance of TNF-α Lpha and leptin in obesity and insulin resistance: a hypothesis on the impact of physical exercise. Exerc Immunol Rev. 1998;4:77–94.
56. Nogueira ME, Sousa Neto IV, Motta-Santos D, Cantuária APC, Lima SMF, Rezende TMB, Santana HAP, Petriz BA, Marqueti RC, Almeida JA. High-protein diet associated with resistance training reduces cardiac TNF-α levels and upregulates MMP-2 activity in rats. Arch Physiol Biochem. 2022;128(6):1630–6. https://doi.org/10.1080/13813455.2020.1787456.
57. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol. 2012;13(4):251–62.
58. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol. 2012;8(8):457–65.
59. Wang Q, Hu J, Liu Y, Li J, Liu B, Li M, Lou S. Aerobic Exercise Improves Synaptic-Related Proteins of Diabetic Rats by Inhibiting FOXO1/NF-κB/NLRP3 Inflammatory Signaling Pathway and Ameliorating PI3K/Akt Insulin Signaling Pathway. J Mol Neurosci. 2019;69(1):28–38. https://doi.org/10.1007/s12031-019-01302-2. PMID: 31111330.
60. Li J, Yu X, Pan W, Unger RH. Gene expression profile of rat adipose tissue at the onset of high-fat-diet obesity. Am J Physiol Endocrinol Metab. 2002;282(6):E1334–41.
61. Carobbio S, Hagen RM, Lelliott CJ, Slawik M, Medina-Gomez G, Tan CY, et al. Adaptive changes of the Insig1/SREBP1/SCD1 set point help adipose tissue to Cope with increased storage demands of obesity. Diabetes. 2013;62(11):3697–708.
62. Vandersmissen J, Dewachter I, Cuypers K, Hansen D. The impact of exercise training on the brain and cognition in T2DM, and its physiological mediators: a systematic review. MedRxiv. 2024;2024–09.
63. Zabetian-Targhi F, et al. The association between physical activity intensity, cognition, and brain structure in people with type 2 diabetes. J Gerontol Biol Sci Med Sci. 2021;76(11):2047–53.

64. Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. Nature. 2008;454(7203):463–9.
65. Pedersen BK. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. Eur J Clin Invest. 2017;47(8):600–11.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.