Brief Report

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# The Effect of Endurance Training on Expression of Autophagy Genes (Beclin-1, ULK-1) in the Heart Tissue of Male Rats with Experimental Diabetes

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## Abstract

**Objective:** This study aimed to investigate the effect of six weeks of endurance training on the expression of autophagy-related genes (Beclin-1, ULK-1) in the heart tissue (Myocardium) of rats with diabetes.

**Materials and Methods:** Twenty male wistar rats (weight: 204±11.3g), (age= 8 weeks) were divided into four groups including: 1) diabetic type1 training, group 2) diabetic type1 control, group 3) healthy training group, and 4) healthy control group. They developed diabetes by intraperitoneal injection of streptozotocin (STZ) (45 mg / kg). The endurance training was performed with a moderate intensity (50-55% vo2max) of 5 days a week for 6 weeks. The expression level of autophagy-related genes (ULK-1, Beclin-1) was measured by real-time technique. One-way analysis of variance and Tukey's post hoc test were used for statistical analysis.

**Results:** The expression of autophagy genes (Beclin-1: diabetic type1 control group: 2.49 (±0.53), and healthy control group: 1 (±0.21)), (ULK-1; diabetic type1 control group: 2.56 (±1.02), and healthy control group: 1 (±0.35)) in heart tissue in diabetic rats was significantly higher than in the healthy control group (*P*: 0.001). After six weeks of endurance training, the expression of these genes in heart tissue was significantly lower in the diabetic training group, healthy training and healthy control than in the diabetic control group. (*P*: 0.001).

**Conclusion:** The present study results showed that endurance training by reducing autophagy factors in the heart of male rats with diabetes could be helpful as a preventive and non-pharmacological agent in the treatment of diabetic patients.

**Keywords**: Endurance training, Beclin-1, ULK-1, Diabetes**,** Heart tissue

QR Code:

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## Introduction

Decreased insulin signaling or insulin resistance leads to impaired glucose and hyper-insulin transport, which negatively affects the structure and function of various organs of the body, including the cardiovascular system (1,2). Researchers are looking for appropriate methods to reduce or modify cell death and subsequent damage.

Since exercise was known for many years as a physiological stimulant that causes metabolic adaptations to health outcomes, and according to research, exercise with different intensities can inhibit or activate autophagy, few studies have been performed on autophagy-related factors in the hearts of diabetic rats, and its underlying mechanisms are not well understood. In the present study, the effect of six weeks of endurance exercise on the expression of autophagy genes (Beclin-1, ULK-1) in the heart tissue of male rats with experimental diabetes was investigated.

## Materials and Methods

In this experimental study, 20 male wistar rats (weight= 204±11.3 g), (age= 8 weeks) were obtained from the experimental animal holding of Shahid Chamran University of Ahavz ,Ahvaz, Iran. All rats were placed under controlled conditions and temperature of 22±3 °C and 12:12h light: dark cycle (awaking cycle started at 16:00). All rats were housed in conventional conditions and fed standard diet and water ad libitum at the animal facility for 1 week before experiments began. For familiarization animals walked on a rodent treadmill 10-15 min at 10 m/min speed 5 sessions/week, 20 rats were divided equally into 4 groups as follows: 1) Diabetic Trained group (TD; n= 5): they did endurance exercise 5 sessions per week for 6 weeks. 2) Diabetic Control (DC; n= 5) group: They were diabetic and excluded from any exercise training. 3) Healthy Trained (HT; n= 5) group: They were involved in the endurance exercise similar to the DT group. 4) Health Control (HC; n= 5) group: They were not involved in any exercise. Diabetes was induced by a single intraperitoneal injection of streptozotoci (STZ, 45 mg/kg) (3,4). Diabetes was confirmed as the blood glucose level higherthan 250 mg/dl (5). Bodyweight was measured weekly.

In the present study, the endurance training was performed based on the research of Chang Huan et al, 2011, first, to get used to the laboratory conditions, the treadmills and the animals were manipulated on the treadmill five days a week for 10-15 min at a speed of 10 m/min. Then, TD and HT were exposed to treadmill training, five sessions per week for six weeks (6). The speed and duration of the treadmill training gradually increased from 10 meters per minute for 10 minutes in the first week, 10 m/min for 20 min in the second week, 14 to 15 m/min for 20 min in the third week, 14 to 15 m/min for 30 min in the fourth week and 17 to 18 m/min for 30 min in the fifth and sixth weeks. To obtain adaptations to a uniform state, all training variables were kept constant in the last week (sixth week).

Expressions of Beclin-1 and ULK-1 genes were measured using the real-time PCR method in the heart tissue of the rats.

Normality and homogeneity were assessed by Kolmogorov-Smirnov and Leven's test, respectively. One-way ANOVA was used to evaluate the significance of the differences between the groups and if it was significant, the Tukey post hoc test was used to determine the differences between the means. Data analysis was performed using SPSS-22 software at a significance level of P-value ≤ 0.05.

## Ethical considerations

An ethics committee approved all experimental protocols of the Shahid Chamran University of Ahvaz for animal and human experiments (EE/99.3.02.59296/scu.ac.ir).

## Results

Data analysis showed that endurance training had an effect on the level of Beclin-1





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gene and reduced the gene level in heart tissue of rats, so that the difference was significant in the diabetic training group compared to the diabetic control group (*P*: 0.001). Moreover, endurance training reduced the gene level of ULK-1 in heart tissue of diabetic rats so that the difference was significant in the diabetic training group compared to the diabetic control group (*P*: 0.001).

## Discussion

The purpose of this study was to investigate the effect of six weeks of endurance training on autophagy genes (Beclin-1, ULK-1) in the heart tissue of diabetic rats. The results showed that moderate intensity endurance training; Prevents abnormal weight loss and hypoglycemia in STZ-induced diabetic rats, and diabetes leads to a significant increase in the levels of autophagy gene (ULK-1, Beclin-1) in the heart tissue of rats. Also, endurance training reduces the levels of autophagy gene (ULK-1, Beclin-1) in the heart tissue of diabetic rats. Consistent with our findings, Jokar et al. 2020, investigated the effect of 4 weeks of high-intensity intermittent exercise on the protein content of 3Oa- and Beclin-1 in the left ventricular tissue of the heart of rats with type 2 diabetes. The results showed a significant decrease in Beclin-1 protein content of the trained diabetic group compared to the diabetic control group (7). Also, the research works of Munasinghe et al. 2016 and Gao, 2015, showed a significant increase in the levels of indicators involved in the process of autophagy following the induction of diabetes compared to the healthy control group (8,9). Jung et al. 2008, showed, lack of autophagy by destroying Atg7 protein in beta cells leads to degradation of islets of Langerhans, accumulation of damaged proteins and decrease in insulin production as well as hyperactivity of mTORC1 protein which increases with oxidation. Mitochondria and ER stress and beta cell defects are associated in animals. Therefore, it seems that a normal and optimal level of autophagy flow is essential for cell homeostasis (10). Also, Jafari et al. (2020) investigated the effect of intense intermittent exercise with and without caffeine on the expression of proteins associated with myocardial autophagy in diabetic rats. The results showed that the expression of all autophagy proteins in the untrained and trained diabetic groups was higher than the healthy group and exercise modulated and reduced the autophagy factors (11). As the results of the present study showed, aerobic exercise as a preventive intervention reduces the increased autophagy parameters due to induction of diabetes to balance the autophagy pathway. Observing the difference in the effects of physical exercise in the present study (reducing role) compared to some of the above studies (increasing role) may be due to the basal state of the tissue under study in the face of various types of stress (e.g. Aging, atrophy and hypoxia) that is the exercise of physical exercise as a protective factor in an effort to establish cellular homeostasis at a normal level and in an emergency. In this study, we were unable to measure other genes involved in autophagy. It is suggested that future research investigate the effect of endurance training and resistance training on autophagy factors in other tissues of diabetic rats.

The present study shows that moderate-intensity endurance activity can have positive and continuous effects on patients with diabetes. Therefore, regular physical activity with moderate or low intensity can be a helpful solution and practical non-pharmacological intervention to control the complications of diabetes. One of the limitations of this study is the lack of simultaneous measurement of tissue in all rats and simultaneous measurement of blood glucose and weight of rats.

## Conclusions

Moderate-intensity aerobic exercise, possibly by modulating hyperglycemic conditions, could be a useful inhibitor to control the overexpression of endoplasmic reticulum oxidative stress factors in the heart



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tissue of male diabetic rats. Such inhibition can prevent the induction of defective intracellular cycles and control stimulatory conditions. In general, the present study shows that moderate intensity aerobic activity can have positive and continuous effects for patients with diabetes. Therefore, regular physical activity with moderate or low intensity can be a useful solution and practical non-pharmacological intervention to control the complications of diabetes.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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