



Original Article

## ***Effect of Adipose Tissue-Derived Stem Cell Transplantation and Six Weeks of Aerobic Exercise on FNDC5 and Irisin Levels in Streptozotocin-Induced Diabetic Rats***

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### ABSTRACT

**Background and objectives:** It has been suggested that irisin and fibronectin type III domain-containing protein 5 (FNDC5) can increase energy expenditure, promote weight loss and improve insulin resistance in diabetic patients by affecting white and brown adipose tissues. In this study, we investigate effect of adipose tissue-derived stem cell transplantation and six weeks of aerobic exercise on FNDC5 and irisin levels in streptozotocin-induced diabetic rats.

**Methods:** Forty-eight rats (weighing 220-240 g and aged nine weeks) were divided into six groups of control, sham, diabetes control, diabetes + exercise, diabetes + stem cell and diabetes + exercise + stem cell. The exercise group ran on running wheel at intensity of 60-70%  $VO_{2max}$ , five days a week for six weeks. Next,  $1.56 \times 10^6$  stem cells extracted from human adipose tissue were injected into the tail vein of streptozotocin-induced diabetic rats. Finally, FNDC5 and irisin plasma levels of the mice were measured using enzyme-linked immunosorbent assay kits.

**Results:** FNDC5 and irisin levels reduced significantly in the diabetes control group ( $P=0.0001$ ). FNDC5 levels in the diabetes + exercise + stem cell and the exercise group increased significantly compared to the diabetes control group ( $P=0.0001$ ). The irisin level in the diabetes + stem cell + exercise group, exercise group and stem cell group increased significantly compared to the diabetes control group ( $P=0.0001$ ).

**Conclusion:** The results indicate that aerobic exercise program and stem cell therapy alone and combined can significantly increase plasma irisin levels. Given the favorable effects of adipose tissue-derived stem cell injection and aerobic exercise on FNDC5 and irisin levels, this strategy could be further evaluated in coping with the adverse effects of diabetes on metabolism and aging.

**Keywords:** Aerobic exercise, Adipose tissue-derived stem cell, FNDC5, Irisin, Diabetes

## INTRODUCTION

Diabetes is a metabolic disorder characterized by hyperglycemia due to a defect in insulin secretion, insulin function or both. The disease is associated with endocrine disorders and metabolic complications (1). Diabetes mellitus has been one of the chief causes of death in the United States over the past few decades. More than half of diabetic individuals are unaware of their condition, which could be a reason for the increased diabetes-associated mortality rates (2). Long-term studies on diabetics demonstrate a 99% and 40-50% reduction in beta cell activity in type 1 diabetes and type 2 diabetes, respectively (3, 4). Diabetes mellitus is involved in the metabolism of brain amyloid and the tau protein. Changes in insulin and glucose hemostasis at the peripheral parts of the body may affect the function of insulin and its receptor, thus leading to increased amyloid-beta oligomerization and tau hyperphosphorylation (5). According to research, irisin and fibronectin type III domain-containing protein 5 (FNDC5) are newly-identified proteins that can increase energy expenditure, promote weight loss and improve insulin resistance in diabetic patients by affecting white and brown adipose tissues (6). Regular physical activity, proper nutrition, limited consumption of alcohol and tobacco products and stress reduction for the benefit of mental health are some of the national health aims pursued by developed countries (7). Although regular physical activity improves the human body's functioning, comprehensive results are needed to further support this claim (8). Several hormones secreted from the adipose tissue and skeletal muscles are responsible for the regulation of energy expenditure and prevention of weight gain and insulin resistance. Irisin, as a unique example of these hormones, is associated with energy homeostasis and subsequently obesity. It exerts considerable direct effects on adipose tissue and is a potential indicator of myocardial infarction (9). This hormone is secreted into the bloodstream through skeletal muscle contraction after cleavage from FNDC5 (9). Studies have shown that regular exercise has a positive impact on irisin and

FNDC5 levels through increased energy metabolism (10, 11). In this regard, a study showed that 10 weeks of endurance training results in a two-fold increase in FNDC5 levels in human subjects (12). Both irisin and FNDC5 are involved in the beneficial effects of exercise on adipose tissue of humans and rodents (13). Sanchez et al. reported that irisin and FNDC5 could increase energy expenditure and maintain normoglycemia (14). In contrast, it has been shown that circulating irisin levels are reduced in trained individuals (15). Irisin is a signaling protein released from the skeletal muscles after proteolysis of the FNDC5 protein through overexpression of *PPAR- $\gamma$*  and uncoupling protein-1 gene (*UCPI*) and other genes associated with the browning of white adipose tissue (16). The level of irisin after exercise varies significantly in mice and human subjects (17). Brown adipose tissue plays a thermogenic role due to *UCPI* expression and increased mitochondrial capacity (18). As a non-pharmacological treatment, exercise plays an influential role in regulating and reducing inflammatory cytokines associated with the production of pancreatic beta cells (19-21). It has been also indicated that both short-term and long-term exercise can decrease blood glucose concentration and insulin resistance and increase beta cell mass through the process of hyperplasia (22-25). Although there is a consensus about the significance of physical activity, the type of exercise to render weight loss and health improvement is not yet clear. However, persistent aerobic exercise at moderate-intensity has been recommended to achieve the best metabolic adaptations (26, 27).

Stem cell therapy is a relatively novel method proposed for the compensation of lost cells (28-30). An interesting source of these cells are mononuclear stem cells derived from adipose tissue that have faster growth rates compared to umbilical cord and bone marrow stem cells (31, 32). In this study, we investigate the interactive effects of aerobic exercise and intravenous injection of adipose tissue-derived stem cells on FNDC5 and irisin

## MATERIALS AND METHODS

The present study was approved by the National Committee for Ethics in Biomedical Research. A total of 48 adult eight-week-old male Wistar rats weighing approximately

220-240 grams were provided. The rats were kept in the rodent laboratory of the Islamic Azad University of Sari for a week to adapt to the environment. All laboratory procedures were in accordance with the standards for the care and use of laboratory animals. At nine weeks of age and after acquaintance with running wheel, the animals were randomly assigned to six groups of healthy control, sham, diabetes control, diabetes + exercise, diabetes + stem cell and diabetes + exercise + stem cell. All groups had ad libitum access to water and food. The animals were kept in groups of four, at temperature of 20-25 °C, under 12:12 h light–dark cycle with a relative humidity of 45-55%.

To induce diabetes in rats, the subjects received intravenous injection of streptozotocin (60 mg/kg). Blood samples were collected from the subjects' tail 72 h after the induction of diabetes. Blood sugar was measured with a glucometer (GM110, Bionime, Switzerland). Subjects with a fasting blood sugar of more than 250 mg/dl were considered as diabetic (30) (Table 1).

To obtain adipose tissue stem cells, adipose samples were taken from the abdominal area of patients referred to the surgery ward of Al-Zahra hospital in Isfahan (Iran) for liposuction procedure. The collected tissue samples were placed in a sterile container and were transferred to the laboratory at room temperature. The tissues were washed with phosphate buffer saline (PBS) containing penicillin-streptomycin four times to make sure the solution is free from blood. The tissues were then digested by collagenase-1 for 90 minutes at 37 °C to separate cells. Next, enzymatic activity and cell plaque were obtained. The remaining red blood cells were lysed with tris-buffered ammonium chloride. The resulting cells were counted, cultured in a

cell culture flask and finally injected into the subjects after fluorescence identification. Cellular expression of CD29 and CD90 was evaluated to determine the phenotype characteristics of the adipose-derived stem cells (30, 33). After induction of anesthesia by intraperitoneal injection of a mixture of 10% ketamine (50 mg/kg) and 2% xylazine (10 mg/kg), the tails were kept in warm water for one minute to dilate the vascular vessels and thus the vein. Next, after washing the cells with PBS, about  $1.56 \times 10^6$  stem cells extracted from the human adipose tissue were injected into the tail vein of diabetic rats with the aid of insulin syringes (30).

The aerobic exercise protocol consisted of running at speed of 10-18 m/min (equivalent to 60-70%  $VO_2$ max) five days a week for six weeks. The speed and duration of exercise increased gradually from 10 m/min for 10 min in the first week to 17-18 m/min for 30 min in the fifth week (34). At the end of the exercise program, the rats were first anesthetized with a 60:40 ratio of ketamine xylazine. Then, 10 ml of blood were collected from the right ventricle into a tube containing EDTA using a syringe soaked in EDTA. The collected blood samples were immediately centrifuged at 1,500 rpm for 10 min to separate plasma. The collected plasma samples were stored in a freezer at -80°C for further measurements. The concentration of FNDC5 and irisin were measured by commercial enzyme-linked immunosorbent assay kits (Hangzhou Co., China) with a sensitivity coefficient of 0.5 pg/mg.

Normality of data was confirmed by the Kolmogorov-Smirnov test. Data were analyzed using one-way analysis of variance (ANOVA) and the Tukey's range test. All statistical analyses were carried out in SPSS (version 20) at significance of 0.05.

**Table 1. The average blood sugar of the groups and confirmation of diabetes in the model groups**

Groups	Average blood sugar (mg/dl)	Standard deviation	Number of rats
Control	113.28	4.42	8
Sham	114.42	4.23	8
Diabetes control	334.71	11.48	8
Exercise + Diabetes	293.57	11.58	8
Diabetes + Stem Cell	334.85	4.70	8
Diabetes + Stem Cell + Exercise	336.42	6.52	8

The irisin level in the diabetes control group decreased significantly compared to the healthy control group ( $P=0.0001$ ). Moreover, the irisin level increased significantly in the exercise + stem cell group compared with the healthy control and diabetes control groups ( $P=0.0001$ ) (Table 3). The irisin level was also considerably higher in the diabetes + exercise group than in the diabetes control group ( $P=0.0001$ ). On the other hand, in the diabetic + stem cell group, there was a significant

increase in the irisin level compared to the diabetes control group ( $P=0.0001$ ) (Figure 2).

## RESULTS

The FNDC5 level in the diabetes control group decreased significantly compared to the healthy control group ( $P=0.0001$ ) (Table 2). In addition, FNDC5 level increased significantly in the exercise + stem cell group compared with the diabetes control group ( $P=0.0001$ ) (Figure 1).

Table 2. Mean level of FNDC5 in the study groups

Group	Mean (ng/ml)	Standard deviation	Minimum	Maximum
Control	2.42	0.51	1.90	2.90
Sham	2.06	0.46	1.70	2.80
Diabetes control	1.35	0.41	1.10	2.00
Exercise + Diabetes	1.98	0.39	1.20	2.50
Diabetes + Stem Cell	1.71	0.50	1.30	1.90
Diabetes + Exercise + Stem Cell	2.00	0.47	1.90	2.30

Table 3. Mean level of irisin in the study groups

Group	Mean (ng/ml)	Standard deviation	Minimum	Maximum
Control	71.00	7.23	65.00	76.00
Sham	70.12	6.70	65.00	74.00
Diabetes control	50.62	4.54	45.00	53.00
Exercise + Diabetes	68.00	5.21	63.00	73.00
Diabetes + Stem Cell	62.87	5.01	60.00	67.00
Diabetes + Exercise + Stem Cell	69.12	5.23	63.00	73.00

Figure 1. Changes in the mean FNDC5 level (ng/ml) in the study groups. \* indicates significant difference with the diabetes control group. # indicates significant difference with the healthy control group.

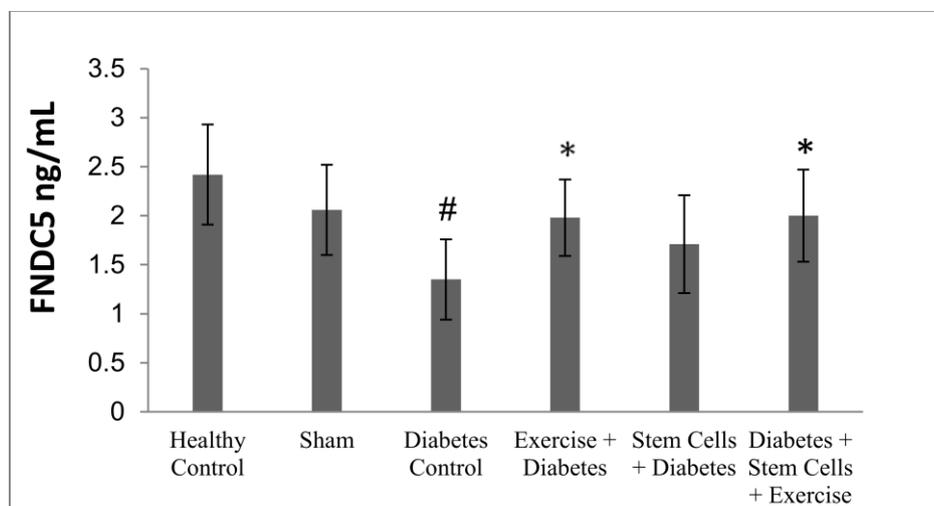
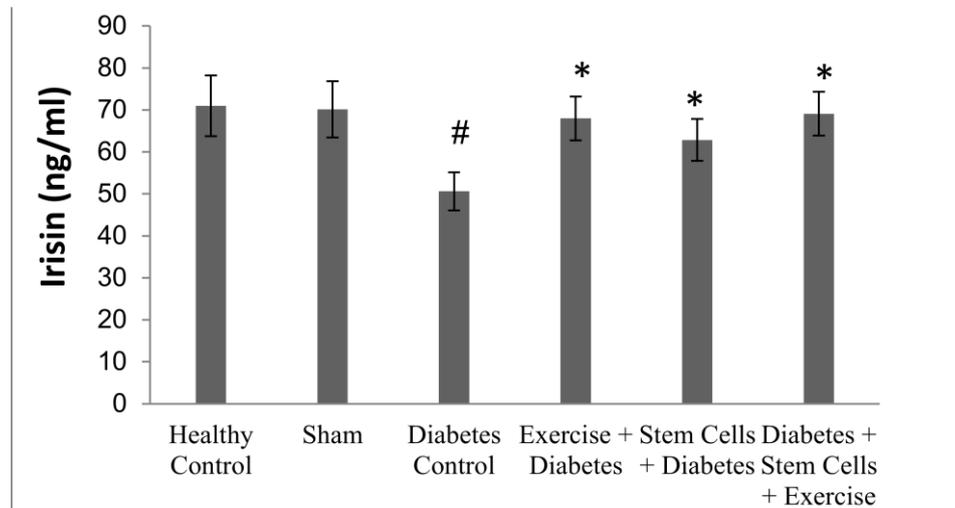


Figure 2. Changes in the mean irisin level (ng/ml) in the study groups. \* indicates significant difference with the diabetes control group. # indicates significant difference with the healthy control group



## DISCUSSION

The main purpose of the study was to investigate the combined effect of exercise along with adipose-derived stem cell injection on diabetic rats. Based on the results, plasma levels of FNDC5 and irisin increased significantly in diabetic mice after the six-week training and adipose tissue-derived stem cells injection. Moreover, the exercise program and stem cell therapy alone and combined significantly increased plasma irisin level compared to the diabetes control group. On the other hand, the FNDC5 levels increased significantly in the exercise group and slightly in the exercise + stem cell group. Thus, it seems that each intervention alone could be a protective factor against the adverse effects of diabetes. Consistent with the results of the present study, it has been shown that 10 weeks of endurance training results in a 2-fold increase in FNDC5 level that in turn affects energy metabolism (12). In a study by Roca et al., short-term training stimulated FNDC5 secretion in subcutaneous and visceral adipose tissues. It was also observed that white adipose tissue could significantly reduce FNDC5 secretion in fasting animals. Interestingly, white adipose tissue of obese animals over-secreted this hormone, which might suggest some kind of resistance because 72% of circulating FNDC5/irisin were previously attributed to muscle secretion. Spiegelman et al. determined that irisin has direct and significant effects on adipose tissue. They also concluded that the exercise-induced irisin

secretion promotes browning of white adipose tissue (16). Sanchez et al. reported that irisin and FNDC5 released from skeletal muscles could increase energy expenditure and maintain normoglycemia (36).

In 2013, Wilson et al. revealed that stem cells isolated from adipose tissue could be differentiated to various cell types to compensate damages to the neurons, cartilage and cardiac cells (37). In a previous study, infection of human adipose tissue-derived stem cells into type 2 diabetic rats resulted in a decrease in blood sugar (38). In the present study, FNDC5 level slightly increased following stem cell therapy, which could be related to the injection-induced stress. In a study on the effects of umbilical cord blood stem cell injection on diabetes, blood sugar level and insulin resistance in adipose tissue of diabetics decreased significantly compared to the control group (39). This can be related to the effects of the milieu in which the stem cells are infused that resulted in secretion of vascular growth factors and cytokines involved in the autocrine or paracrine signaling (40). In line with the present study, another study demonstrated that adipose tissue-derived stem cell transplantation could repair corpus striatum mainly through an increase in vascular endothelial growth factor levels and the angiogenesis process (41).

Increase in vascularity of adipose tissue can in turn increase the access of adipose tissue to metabolic hormones, oxygen and nutrients as well as increased insulin sensitivity.

## CONCLUSION

Given the favorable effects of adipose tissue-derived stem cell injection and exercise on FNDC5 and irisin levels, this strategy could be further evaluated in coping with the adverse effects of diabetes on metabolism and aging.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding publication of this article.

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