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Original Article

Investigation the effect of two models HIIT on IGF-1R gene expression in the left ventricle of rats with type 2 diabetes

Atiye Sadat Mirahmadian Baba Ahmadi [1*], Niku Khosravi [2], Maryam Delfan [3]

1Department of Sport Physiology, Faculty of Sport Sciences, Alzahra University, Tehran, Iran. 2 Faculty member, Department of Sport Physiology, Faculty of Sport Sciences, Alzahra University, Tehran, Iran, 3 Faculty member, Department of Sport Physiology, Faculty of Sport Sciences, Alzahra University, Tehran, Iran.

Correspondence: Atiye Sadat Mirahmadian Baba Ahmadi: Department of Sport Physiology, Faculty of Sport Sciences, Alzahra University, Tehran, Iran.

ABSTRACT

Of major problems of diabetes, one can refer to DCM, which is associated with increased glucose, apoptosis, decreased IGF-1R gene expression. The beneficial effects of High Intensity Interval Training (HIIT) on the expression of these two genes and the level of glucose and diabetic cardiomyopathy were already confirmed in the past. Hence, the present study investigated the way two types of HIIT are implemented to determine the most optimal type of training. For this, 24 male Wistar rats with an average weight of 320±10 g were selected and divided into four groups: normal control (NC), diabetic control (DC), diabetic-HIIT1 with equal interval's time (2 minutes) and diabetic-HIIT2 with low intensity interval's time half the high intensity interval's time (1 and 2 minutes, respectively). Pearson correlation was used to evaluate the relationship between glucose and IGF-1R factors. For normalcy of data, Shapiro–Wilk test was used and for homogeneity of variance, Levene's test was used. Significance level was $\alpha = 0.05$ in all stages. The results indicated that of IGF-1R gene the expression increased in both types of HIIT compared to the diabetic control group. Glucose levels also declined. However, no difference was noted between the effectiveness of both types of training. As a result, one can say that both types of HIIT are found to be effective in improving glucose and IGF-1R gene expression. However, no difference was observed in the IGF-1R gene expression between HIIT1 and HIIT2. Therefore, it is suggested that enough time be allotted for the sick and disabled people (diabetics) to take rest when performing HIIT so that they can practice for a longer period of time.

Keywords: IGF-1R, HIIT, Glucose, Diabetic cardiomyopathy.

Introduction

Diabetes is currently seen a severe public health problem. It has quadrupled in the past three decades, ranking nine in the world in terms of mortality. Cardiovascular complications are also found to be one of the most common causes of mortality in diabetic patients [1, 2]. DCM is a complicated consequence of insulin deficiency, thyroid hormone deficiency, and the sympathetic nervous system being activated. It is widely accepted that DCM is characterized by a set of structural and functional disorders in diabetic patients' hearts. Of these disorders, one can refer to diastolic and systolic contraction, cardiomyocyte hypertrophy and apoptosis, as well as myocardial fibrosis [3].

Apoptosis causes myocardial cells to die in various heart injuries including DCM which is one of the causes of moralities in diabetes. The apoptosis mechanism is one of the main ways to remove unwanted cells that is activated in the body of cellular and even single-celled organisms. Myocardial cell death is an important factor for cardiac pathogenesis as it leads to loss of contractile units, conduction disorders, compensatory cell hypertrophy and heart fibrosis. Cardiac cell death can happen through necrosis (cell response to severe injury) or apoptosis (genetically programmed cell death).

On the other hand, insulin-like growth factor receptor type 1 (IGF-1R) is a growth factor receptor tyrosine kinase with 70% homology along with the insulin receptor (IR). This gene is basically a single receptor used by cells that serves as a vital mediator of cell proliferation and survival. The IGF-1 anti-apoptotic effects occur through interaction with its receptor (IGF-1R). Active intracellular signal transduction pathway is thought to be activated that can regulate mitochondrial and

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cytochrome fluxes. IGF-1R concentrations lead to massive cancer cells apoptosis [4, 5]. Studies have demonstrated that training prevents left ventricular apoptosis and myocyte loss as well as decreased cardiac glucose metabolism leading to DCM, increasing ischemic tolerance and myocardial infarction in the heart of type 2 diabetic rats. This is while physical activity has been described as a means for treating diabetes and cardiovascular disease [6] Wei et al. (2000).

Most of national and international health organizations and communities have introduced physical activity or training as a treatment for obesity, diabetes, and for preventing cardiovascular disease [6].

High Intensity Interval Training (HIIT) can be described as "short intensive activity interval or short activity or rest intervals", which leads to a severe physiological response while indicating a strong cardiac response to continuous moderate training. HIIT is aimed to increase the intensity of the activity so that the participant is not able to continue training for long periods. Thus, rest should be enough for the person to be able to continue for a long time.

Clinical studies in humans strongly endorse the link between insulin resistance and HF without ischemia. Insulin resistance is very common in the HF population without ischemia [7]. Therefore, it is necessary to compare the two types of HIIT o reduce insulin resistance and lower blood sugar levels in order to find the most optimal type of training.

In the present study, attempts were made to discuss the effect of two HIIT procedures on this factor and its receptor by inducing type 2 diabetes in laboratory rats.

Research Method

The present study was of an experimental study carried out in a field and laboratory survey. The study was done on 24 Wistar rats (prepared by Razi Research Institute) with an average weight of 320±10 g; ethical principles related to the research were observed in accordance with the working principles on laboratory animals.

Keeping the animals

All three rats were kept at Tarbiat Modarres University's animal house in separate cages made of transparent polyethylene, under standard conditions of laboratory animals (temperature 22±2 ° C; humidity 45-50%, light-dark cycle 12:12). During the study, rats were fed under standard pellets specific of laboratory mice without any restrictions.

Training protocol

To administer two types of HIIT1 and HIIT2 training, rats were placed into 4 equal groups (n = 6):

1. Normal (Healthy) Control Group (NC): To research all complications except for diabetes;
2. Diabetes Control Group (DC): To investigate the effects of diabetes;
3. HIIT1 and Diabetic Group (HIIT-1): To research the effects of HIIT1 on diabetes;
4. HIIT2 and Diabetes Group (HIIT-2): To investigate the effects of HIIT2 on diabetes;

Therefore, as many as 24 male Wistar rats with average weight of 320 ±10 g) were purchased from Razi Institute of Tehran and transferred to the Animal Laboratory at Tarbiat Modarres University. They were then randomly placed into 4 groups; one healthy and normal group and the other 3 groups were exposed to induced diabetes.

For this purpose, 24 Wistar rats were purchased from the Razi Research Institute in Tehran. The number of six rats were randomly separated as a non-diabetic control group while 18 of these mice were made diabetic by intraperitoneally injecting of 120 mg/kg body weight of nicotinamide dissolved in normal saline (IP) and IP injecting of 60 mg/kg body weight (mg/kg dissolved in 0.05 mol citrate buffer) after 15 minutes as well as injecting of streptozotocin in the second week after 12 hours of overnight fasting. One week after injection, rat blood glucose was measured by a glucometer to confirm diabetes (Japanese zero one) after 12 hours of overnight fasting. The fasting diabetic index of these rats was considered to be 300, which was achieved in all rats and the rats were confirmed to have been made diabetic. These rats were then randomly placed into three groups: diabetic control, HIIT1 and HIIT2. In the present study, by type 1 intense interval training (HIIT1) it is meant a model of interval training in which high-intensity interval training is equal to the rest time between the intervals and both are 2 minutes for five days a week continuing until four weeks. Type 2 Intense interval training HIIT2 is also a model of interval training in which low-intensity interval training is half the time of high-intensity interval training for 1 minute and 2 minutes, respectively, for five days a week as continues up to four weeks. The maximum oxygen consumption was measured once every two weeks on the sixth days. Once in every two weeks, 1 to 2 days were considered for rest. The control groups did not participate in any sports activities. The hearts of all four groups were taken out of the rat's body after blood sampling was done, and the left ventricular tissue of the heart was immediately removed and stored for further analysis. An expression of research variables was assessed in the laboratory by qReal time PCR.

Preparing tissue samples

First, the samples were removed of the fridge state and stored at room temperature for some time. Then, the samples were weighed and about 50 mg of each sample was coded in 1.5 microtubes. The samples were placed on ice to do the remaining work.

Assessment of research factors

qReal-Time PCR

In this study, qReal-Time PCR technique was used to examine changes in IGF-1R gene expression. For this, RNA of the heart

(left ventricle) was first extracted and then treated with DNaseI in a process called DNase I treatment. In this technique, DNA is removed if there is extra DNA in the sample. Finally, cDNA was constructed and qReal-Time PCR reactions were carried out.

cDNA synthesis for IGF-1R gene expression

At this stage, 2 micro liters of random primer was added to the DNase Treatment reaction product containing 11 µl of RNA and placed at 65 ° C for 10 minutes. At the incubation time ended, the reaction product was placed on ice and 5X Reaction Buffer, RiboLock Rnase Inhibitor (20 u/µl), 2 µl of dNTP Mix and 0.5 µl of RevertAid M-Mul Reverse Transcriptase (200 u / µl) were added to each microtube and they were placed in a Corbett thermocycler. The temperature and reaction time according to the kit were as follows: 25°C for 10 minutes, 50°C for one hour, 85°C for 5 minutes, and finally the reaction product was maintained at -80°C for the following reactions.

Designing primer for IGF-1R gene expression

The primers were developed by Nika Zistzhen. It should be stated however that the GAPDH gene was used as an internal control to normalize the reaction.

The qReal-Time PCR reaction was carried out in the same manner to investigate the changes in the target genes expression. GAPDH gene was used for internal control and for quality control of the product. The GAPDH reaction of the sample was transferred onto 2% gel and the presence or absence of the product was examined.

Table 1- shows Real-Time PCR temperature cycle

Variable	Cycles	Duration of each cycle	Temperature
GAPDH, IGF-1R gene expression	1	15 minutes	95°C
	40	15 seconds	95°C
		60 seconds	60°C

Quantifying target gene expression values

The formula 2-ΔΔct(with a negative power ΔΔct) was used to quantify the desired gene expression.

In this formula, the necessary dimensions were obtained through the following steps and placed in the formula as the fold change values were calculated.

Plasma glucose measurement

Plasma glucose was measured by glucose oxidase technique and quantitative plasma glucose detection kit developed by Pars Azmoon Company, Iran with a sensitivity of 5 mg/dL.

Data analysis method

In the descriptive statistics part, such dispersion indices as standard deviation, mean and graph were used. Inferential statistics was also used. Tukey's post hoc test was used to determine the significant position and Pearson correlation was applied to evaluate the correlation between glucose and IGF-1R. Significance level was considered $\alpha = 0.05$ for all statistical tests.

Statistical analyzes were done using SPSS software version 24 and graphs were drawn by Graph Pad Prism software version 8.

Results

Data Description

Table 2- shows the mean and standard deviation of weight and glucose values in four groups.

Variable	(HIIT-1)	(HIIT-2)	(DC)	(NC)
Weight (g)	319.26±00.83	328.18±66.35	324.44±800.21	318.22±33.69
Glucose (mmol/l)	27.1±30.85	25.2±88.62	31.3±51.47	10.0±30.70
IGF-IR gene expression (mg/ml)	3.44±0.44	3.79±1.09	100. ±0.00	5.02±2.69

Data in Table 2 indicate that:

The highest weight relates to the DC group with 324.11±800.21 g and the lowest to the HIIT-1 group with 319.26±00.83 g. Concerning glucose levels as provided in the table, the highest glucose level relates to the DC group with 31.51±3.47 mm / ml and the lowest to the NC group with 10.0±30.70 mg/l. As shown in Table 1, the highest value of IGF-1R with 5.02± 2.69 mg / ml belongs to the NC group and the lowest value relates to the DC group with a level of 1.00 ± 0.00 mg / ml.

Hypotheses Testing

First hypothesis:

There is no significant difference between High Intensity Interval Training type 1 (HIIT-1) and High Intensity Interval Training type 2 (HIIT-2) on IGF-1R gene the expression in the left ventricle of the heart of rats with type 2 diabetes.

According to the results from one-way analysis of variance, in table 3 the effect of the group on IGF-1R gene expression was significant.

Table 3- shows the results of one-way analysis of variance test to determine the effect of group on IGF-1R gene expression values

Changes in IGF-1R gene expression (mg/ml)	sum of squares (ss)	variation range (df)	Mean squares (MS)	fault (F)	Significance level (sig)
Intergroup changes	51.125	3	17.042	7.801	0.001
Intragroup changes	43.690	20	2.184	.....	.....
Total	23	94.815	.....	.....	.....

F120/794=7/801, P=0/000=0/001,η =0/858

Since the group factor has created a significant difference in the level of IGF-1R gene expression, the results from the Tuckey's test are provided to determine the mean inter-group difference. That shown in table 4

Table 4- shows the illustrates the results of the Tuckey post hoc test to specify the mean comparison difference between groups for IGF-1R values

Variable	Group	Groups	M.D.	S.E.	Sig.
IGF-1R gene expression (MG/ML)	Normal control group (NC)	HIIT-1	1.5767*	0.85333	0.001
		HIIT-2	1.2250	0.85333	0.493
		DC	4.0217*	0.85333	0/001
	Diabetic control group (DC)	HIIT-1	-2.4450*	0.85333	0.044
		HIIT-2	-2.7967*	0.85333	0.281
		NC	-4.0217*	0.85333	0.001
	high Intenssity interval training group (HIIT-1)	HIIT-2	-0.35167	0.85333	0.973
		DC	-2.44500*	0.85333	0.044
		NC	-4.2167*	0.85333	0.001
	high Intenssity interval training group (HIIT-2)	HIIT-1	0.3517	0.85333	0.976
		DC	2.7967*	0.85333	0.018
		NC	-1.2250	0.85333	0.493

As table 4 post hoc tuckey's test results were used to provide the main effect of training and to determine the difference between mean group comparisons on changes in IGF-1R gene expression levels. Based on the findings, both HIIT-1 and HIIT-2 training groups increased the IGF-1R gene expression levels compared to DC group's (P = 0.04) and (P = 0.018). However, no significant difference was noted between the two training groups. Both types of training were found to be equally effective in increasing IGF-1R gene expression. According to this hypothesis there is a significant difference between a High Intensity Interval Training type 1 (HIIT-1) and High Intensity Interval Training type 2 (HIIT-2) on the IGF-1R gene expression in the left ventricle of rats with type 2 diabetes, confirmed with 95% confidence. Therefore, the main effect of the training is presented by the effect size table 5 and figure 1.

Table 5- shows the effect size of exercise on the expression of IGF-1R gene.

Univariate test	(SS)	(df)	(MS)	(f)	(sig)	(PSE)
contrast	51.125	3	17.042	7.801	0.001	0.539
Error	43.690	20	2.184			

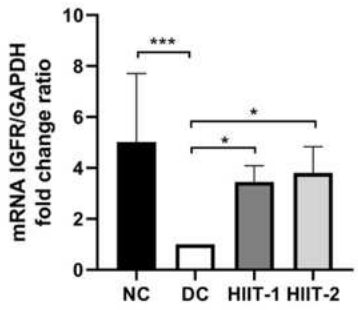

Figure 1 illustrates the ratio of IGF-1R gene expression to GAPDH in four groups. Sign (*) sign 0.05, (**) sign 0.01 and (***) sign 0.001 indicate significance in both exercise group and normal control group compared to diabetic control group.NC: normal control, DC:diabetic control ,HIIT-1: high intensity interval type 1: equal tim(2 min), HHIT-2: high intensity interval type 2 (high intensity 2min, low intensity 1min)

Second hypothesis:

There is no significant difference between High Intensity Interval Training type 1 (HIIT-1) and High Intensity Interval Training type 2 (HIIT-2) on glucose index in rats with type 2 diabetes.

The results from one-way analysis of variance indicated that the effect of group on glucose index was significant.

F2361/451=90/090, P= 0/000=0/000,η =0/992

Since the group factor brought about a significant difference in the amount of glucose, the Tuckey's post hoc test was applied to determine the mean differences between the groups. The results indicated that no significant difference was observed between the two training groups, i.e., HIIT-1 and HIIT-2 (p=0.733). Therefore, the hypothesis stating no significant effect was seen on left ventricular glucose levels in rats with type 2 diabetes between a high intensity interval training type 1 (HIIT-1) and high intensity interval training type 2 (HIIT-2) has been met with 95% confidence. Accordingly, the main effect of the exercise is presented by the effect size table 6 and figure 2.

Table 6- shows the effect size of exercise groups on plasma glucose levels.

Univariate test	(SS)	(df)	(MS)	(f)	(sig)	(PSE)
Contrast	1549.681	3	0.472	516.560	0.000	0.931
Error	114.676	20	5.734			

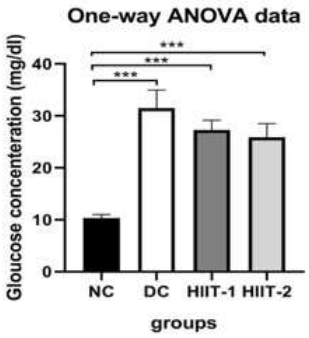

Figure 2 illustrates the ratio of glucose level in four groups. Sign (*) sign 0.05, (**) sign 0.01 and (***) sign 0.001 indicate significance in both exercise group and normal (healthy) control group compared to diabetic control group.NC: normal control, DC:diabetic control ,HIIT-1: high intensity interval type 1: equal tim(2 min), HHIT-2: high intensity interval type 2 (high intensity 2min, low intensity 1min)

Conclusion and Discussion

Diabetes has become an epidemic and is thought of a major threat to global health.

Clinical studies in people with diabetes suggest that heart failure is much higher in diabetic people than in healthy people. In people with diabetes, myocardial dysfunction in the absence of common cardiovascular disease, valvular disease, and other cardiovascular risk factors such as hypertension and dyslipidemia, has led to the descriptive term "DCM."

According to studies, apoptosis is causes cardiomyopathy [8]. IGF-1 and IGF-1R gene expression have also been found to have strong anti-apoptotic properties as they save cells from apoptotic death[16-17]. Research on the cases mentioned demonstrated that HIIT has a high impact on cardiomyopathy than endurance training [9-11].

Since tat no research has ever investigated the most optimal model of intense interval training on apoptosis and DCM, this study aimed to to compare the two HIIT performance types on two IGF-1R genes expression of and glucose levels in the rats with type 2 diabetes having cardiomyopathic heart.

After the data were analyzed and tested and the hypotheses were tested, the research findings suggested:

A. There is no significant difference between High Intensity Interval Training type 1 (HIIT-1) and High Intensity Interval Training type 2 (HIIT-2) on the GF-1R gene expression in the left ventricle of rats with type 2 diabetes.
B. There is no significant difference between High Intensity Interval Training type 1 (HIIT-1) and High Intensity Interval Training type 2 (HIIT-2) on glucose index in rats with type 2 diabetes.
C. There is no significant correlation between glucose levels and IGF-1R expression after High Intensity Interval Training type 1 (HIIT-1) and High Intensity Interval Training type 2 (HIIT-2) in the left ventricle of rats with type 2 diabetes.

The present study demonstrated that the IGF-1R gene expression significantly increased compared to the DC group after 4 weeks of HIIT1 and HIIT2 in the left ventricle of cardiomyopathic hearts of diabetic rats. As well, the IGF-1R gene expression was higher in HIIT2 than in HIIT1; however, this rise was not significant. Perhaps the reason for this was the insufficient difference between the two protocols or the interval timing. Glucose levels also decreased in HIIT1 and HIIT2 compared to the DC group, but this amount was found to be higher than the NC group.

Marcinko et al. (2015) investigated the impacts of 6 weeks of HIIT training using obese mice, resulting in lower blood sugar levels as insulin sensitivity to fat and liver improved. As a result, this study was found to be consistent with the present study [12].Verboven et al. (2018) divided 32 mice into two groups: simple diet as a control group (10 mice) and high-sugar diet as a diabetic group (22 mice) [13].

The diabetic group was itself divided into three groups: inert group (8 mice), HIIT (7 mice). Factors were measured after 30 weeks and indicated that both types of training caused glucose and insulin levels to normalize independent of the normal exercise method. End-diastolic pressure increased in inert diabetic animals, but returned to normal after the training was performed. Besides, hypertrophy reduced the LV wall. Finally, FS improves only through moderate-intensity training in which the state of inflammation in the heart tissue decreases. As a result, both types of training modify the extent of DCM complications equally. However, moderate-intensity training appears to reduce cardiac inflammation [13].

In a study on 13 male HF patients performing training for 12 weeks and 3 sessions each week, Tezanis et al. (2017) found out that training with severe to low ratio of 4 to 3 in 80% and 50% VO2peak and analysis on muscle fiber type , CSA and capillary density, mRNA, insulin-like growth factor-1 (IGF-1) and its isoforms (eg IGF-1Ea, IGF-1Eb, IGF-1Ec), insulin-like growth factor receptor-1 (IGF-1R) and protein-bound (IGFBP-3) indicted increased expression of IGF-1Ea, IGF-1Eb, IGF-1Ec and IGFBP-3. The amount of type 1 fibers and the capillary to fiber ratio also rose. As a result, they found that HIIT reverses skeletal myopathy in HF patients, which may arise from adaptive responses of the IGF-1 aggregation system [14].

Tartibian et al. (2018) conducted a survey on 22 male volunteers divided into two groups of training and inert/inactive groups; they performed HIIT for 30 minutes 3 days a week for 8 weeks in a training group. The findings demonstrated that serum IGF-1 levels in the training group rose significantly after 8 weeks of HIIT training compared to the initial condition and the control group. One can argue that HIIT has no significant effect on increasing the level of IGF-1 secretion in the liver as it leads to the IGF-1 activation inhibition and the IGF receptor signaling pathway stimulation [15].

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