Original Article

On investigating the effect of two high intensity interval training models (HIIT) on IGF-1 gene expression in the left ventricle of rats with type 2 diabetes

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Abstract

Apoptosis causes diabetic cardiomyopathy. The IGF-1 gene has an anti-apoptotic effect. The beneficial effects of High intensity interval training (HIIT) on the expression of the two genes mentioned and the glucose level as well as diabetic cardiomyopathy have been substantiated in the past. Hence, the present study investigated the administration of two types of HIITs in order to determine the most desired type of training. For this end, 24 male Wistar rats with a mean weight of 320±10g were selected. Mice were then divided into four groups, i.e. normal control (NC), diabetic control (DC), diabetic-HIIT1 with equal interval times (2 minutes) and diabetic-HIIT2 with low-intensity interval half the high-intensity interval (1 and 2, minutes) respectively. Diabetes was induced through injecting streptozotocin-nicotinamide (STZ-NA). The rats fainted after running on the treadmill for four weeks. The left ventricle was then removed and frozen in liquid nitrogen, and finally glucose levels and IGF-1 and IGF-1R gene expression were measured. The findings demonstrated that IGF-1 gene expression saw an increase in both types of training (HIIT) compared to the diabetic control group. Glucose levels also decreased. But no difference was noted between the effectiveness of both types of training. As a result, one can say that both types of HIIT are effective in improving glucose and IGF-1 gene expression. However, administering the two types of HIIT, one with an equal interval time and another HIIT with low intensity interval half of the high intensity interval in the IGF-1 revealed no difference. Therefore, it is recommended that enough time is set for rest when conducting HIIT in sick and disabled people (diabetics), so that the person can practice for a longer period of time.

Keywords: IGF-1, HIIT

Introduction

Diabetes is a metabolic disorder that has become a prevalent and serious problem across the world today. It is a chronic disease caused by hyperglycemia which is associated with such complications as microvascular diseases of the eyes and kidneys and all kinds of clinical neuropathies. Researches at a global scale have suggested that this disease can be diagnosed through measuring glucose and insulin levels. It is estimated that the number of patients will increase to 642 million by 2040. Diabetic conditions cause a high risk of cardiovascular diseases and may leave a direct negative effect on the myocardium. These negative effects of diabetes on the heart leading to diabetic cardiomyopathy (DCM) were largely surveyed in the past three decades.

Diabetes Mellitus (DM) causes abnormal changes to the structure of various organs of the heart, including the plasma membrane and other cardiovascular cytoplasmic organs (1). DCM is a complex consequence of insulin deficiency, deficiency of thyroid hormone, and activated sympathetic nervous system (2). Over the past three decades, a number of epidemiological, autopsy, animal, and clinical studies have recognized the presence of diabetic heart disease as a distinct clinical entity.

Increased glucose causing apoptosis is seen one of the most important factors of cardiovascular disease that leads to mortality and diabetes-related complications (3). Apoptosis causes such complications as loss of contractile units, disturbances with conduction, compensatory hypertrophy of heart cells, and fibrosis. However, different IGF-1 pathways

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How to cite this article: Mirahmadian Baba Ahmadi, A. S., Khosravi, N., Delfan, M. On investigating the effect of two high intensity interval training models (HIIT) on IGF-1 gene expression in the left ventricle of rats with type 2 diabetes. Arch Pharma Pract 2020;11(S4):85-90.

perform anticoagulant and anti-apoptotic actions. Glucose causes a disruption to mitochondrial function, cytochrome C release with apoptosis being blocked by IGF-1. In sum, the data have demonstrated that IGF-1 inhibits glucose-caused impairment of mitochondrial function, cytochrome C release, and apoptosis (4).

Insulin-like growth factor 1 and 2 (IGF-2 and IGF-1) are expressed at high levels in the pancreatic endocrine gland during tissue growth and reconstruction. This is while, they have weak effects on the endocrine glands of the pancreas (5). IGF-1 is a protein encoded in humans by the IGF-1 gene. This molecule performs several biological activities similar to insulin. IGF-1 concentration varies by age, nutritional status, body composition and physical activity (6).

Diet and training are seen as the two main integral elements of health considered to be non-pharmacological treatments for diabetes because training improves blood sugar and cardiovascular function and increase insulin sensitivity using glucose as the main metabolism. As a result, it is considered to be one of the most effective ways to reduce the incidence of cardiovascular diseases and reduce the pace rate of cardiomyopathy (7). On the other hand, physical activity has been accepted as a key element in preventing type 2 diabetes; besides, it is suggested that low aerobic activity is associated with higher mortality rates in diabetic populations. Wisloff et al. (2001) stated that training therapy is an important non-pharmacological treatment for diabetes and DCM as it enjoys high effectiveness and low rate of complications (8) which may be partly attributed to improved patients' aerobic training capacity (9).

High Intense Interval Training (HIIT) is a type of training that involves intense short-term repetitions with short rest or recovery periods whose impact on the cardiovascular, pulmonary, and muscular systems has led scientists to study it. In sum, HIIT is regarded as a safer and more tolerable therapy for the patient than regular trainings. In general, the central and environmental compatibility made through HIIT have been proven in animal and human models. It is also found to be more effective than endurance and continuous training.

In general, research findings suggest favorable changes in glucose, IGF-1, IGF-1R, cardiomyopathy, HF, insulin resistance and diabetes-related factors as a result of physical activity as they involve a wide range of factors. First physical activity and then endurance training that takes a long time were found to leave some positive effects on these factors. However, because of HIIT, this type of training enjoys a high position in terms of time and favorable effects on regulating fasting glucose, insulin resistance, diabetes, DCM and IGF-1 expression. This is despite the fact that no optimal method is yet to be found for performing HIIT and no time ratio is focused for high and low intervals, and in different studies this ratio varies from 1-1 to even 3-4.

As a result, the study on the most favorable HIIT procedure in the IGF-1 and IGF-1R genes expression is critical. This is when, some studies have shown that continuous training has been successful in controlling glucose more than HIIT. On the other hand, AIT was reported to be more effective than MCT in improving VO2peak in patients with HF as it reduces the CAD-induced discharge fraction as well as other causes. Weight loss, increased cardiovascular respiratory function, improved heart function in training, and myocardial function are more common results of this procedure. But, moderate-intensity training has been reported to adjust DCM complications to the same extent against HIIT (10 - 17).

Over the past decade, high-intensity interval training (HIIT) has received much attention as advocates claim that this training, despite reduced time commitment, can yield significant health benefits over moderate-intensity continuous training (11). Recent evidence from Elliott et al. on healthy participants, patients with heart failure, and patients with cardiovascular disease indicates that intense interval training may be regarded as an effective strategy for improving aerobic capacity over moderate-intensity regular training (9, 19).

According to researches done in this field, intense interval training has many beneficial and positive effects on diabetes and diabetic diseases. Despite this, studies are yet to find the most desired type of training. Therefore, this study aimed to find the most desired intense interval training. Following this, the effect of two types of intense interval training was investigated so that the researcher can answer the following question.

Which of the two types of exercise (HIIT) yields better results or effects one with equal activity or rest time or twice the rest time?

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. 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 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.

Assessing research factors

qReal-Time PCR

In this study, qReal-Time PCR technique was applied to investigate the changes in IGF-1 and IGF-1R gene expression. For this, first RNA of the heart (left ventricle) was removed and then treated with DNaseI during a process called DNase I treatment. In this procedure, DNA is deleted if there is extra DNA in the sample. Finally, cDNA was constructed and qReal-Time PCR reactions were made.

cDNA synthesis for IGF-1 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-1 and 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 (Figure 3-6).

Table 1: Real-Time PCR temperature cycle

Variable	Cycles	Duration of each cycle	Temperature
GAPDH,	1	15 minutes	°C95
IGF-1 gene expression	40	15 seconds	°C95
		60 seconds	°C60

Quantifying target gene expression values

The formula $2^{-\Delta\Delta ct}$(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.

Measuring plasma glucose

Plasma glucose was assessed by glucose oxidase method and by plasma glucose quantification detection kit made by Parts company in Iran with a sensitivity of 5 mg/dL.

Data analysis method

In the descriptive statistics section, the dispersion indices of standard deviation, mean and graph were applied. Inferential statistics was used. Tukey post hoc test was applied to determine the significant position while Pearson correlation was used to evaluate the correlation between glucose with two IGF-1 and IGF-1R factors. Significance level was regarded as $\alpha = 0.05$ for all statistical tests. Statistical analyses were performed using SPSS software version 24 and graphs were plotted by Graph pad prism software version 8.

Results and Findings

Data description

Table 2: The mean and standard deviation of IGF-1 gene expression values in four groups

Groups	Intense interval training Group Type 1 (HIIT-1)	Intense interval training Group Type 2 (HIIT-2)	Diabetic control group (DC)	Healthy control group (NC)
Gene expression (mg/ml) IGF-1	2.930±70.	3.35±1.03	001.00±0.00	4.53±1.73

As seen in Table 2, the highest levels of IGF-1 gene expression are related to the NC group with 4.53± 1.73 and the lowest value is related to the DC group with 11.0±00.00mg / ml.

Testing hypotheses

There is no significant difference between a period an intense interval training type 1 (HIIT-1) and intense interval training type 2 (HIIT-2) on the expression of IGF-1 gene in the left ventricle of rats with type 2 diabetes.

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

F183 / 161 = 11/320, P = 0/000 = 0/000, η = 0.902

Since the differences between the groups indicate the main effect of the training, the results related to the Tuckey test are summarized in Table (3) to determine the point of the difference between the mean comparisons of the groups on changes to the IGF-1 gene expression..

Table 3: illustrates the results of the Tuckey post hoc test to specify the mean comparison difference between groups for IGF-1 values

Variable	Group	Groups	M.D.	S.E.	Sig.
IGF-1 gene expression (MG/ML)	Healthy control group (NC)	Intense interval training group (HIIT-1)	1.6017	0.61801	0.076
		Intense interval training group (HIIT-2)	1.1800	0.61801	0.256
		Diabetic control group (DC)	3.5367*	0.61801	0.000
	Diabetic control group (DC)	Intense interval training group (HIIT-1)	-1.9350*	0.61801	0.025
		Intense interval training group (HIIT-2)	-2.2567*	0.61801	0.006
		Healthy control group (NC)	-3.5367*	0.61801	0.000
	Intense interval training group (HIIT-1)	Intense interval training group (HIIT-2)	0.4217	0.61801	0.903
		Diabetic control group (DC)	1.9350*	0.61801	0.025
		Healthy control group (NC)	-1.6017*	0.61801	0.073
	Intense interval training group (HIIT-2)	Intense interval training group (HIIT-1)	0.4217	0.61801	0.903
		Diabetic control group (DC)	2.2567*	0.61801	0.006
		Healthy control group (NC)	-1.1800	0.61801	0.256

As Table 3 shows, the expression level of IGF-1 gene in both training groups was significantly increased compared to the DC group. So that its values in HIIT-1 group was P = 0.025 and P = 0.006 in HIIT-2 group while no significant difference was seen in IGF-1 gene expression values between both training groups with NC group, (P = 0.903) and (P=-0.76) 0P) respectively. The findings indicate that both training groups similarly led to increased IGF-1 gene expression. Therefore, the assumption stating no significant difference exists between an intense interval training of HIIT -1 and intense interval training of HIIT-2 is accepted with 95% confidence.

Therefore, the main effect of the exercise is shown in Figure 1.

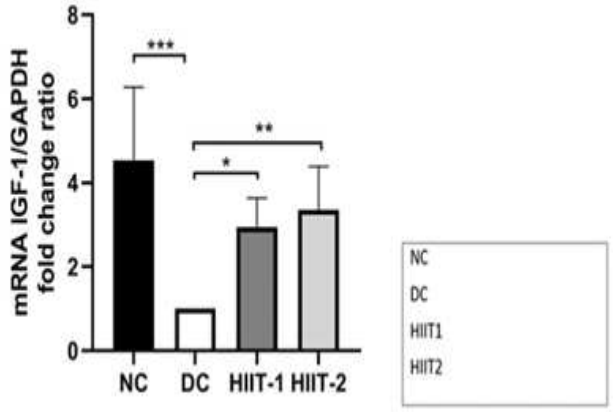

Figure 1: illustrates the ratio of IGF-1 gene expression to GAPDH in four groups. Sign (*) sign 0.05, (**) sign 0.01 and (***) sign 0.001 indicate significance in both exercise group and healthy control group compared to diabetic control group.

There is a significant correlation between glucose levels and IGF-1 gene expression after an intense interval training of type 1 (HIIT-1) and intense interval training of type 2 (HIIT-2) in the left ventricle of rats with type 2 diabetes.

Table 4: The correlation between glucose levels and IGF-1 gene expression after a training session.

		Glucose	IGF-1
IGF-1 gene expression	Pearson correlation	-0.8755*	1
	Sig. value	0.0223	

As shown in Table 4, in the HIIT-1 training group, there is a significant negative relationship between reduced glucose and increased IGF-1 gene expression. Decreasing glucose levels increased IGF-1 gene expression (P = 0.0223) (r = 8755). Based on this hypothesis there is no significant correlation between glucose levels and IGF-1 gene expression after an intense interval training type 1 (HIIT-1) and intense interval training type 2 (HIIT-2) in the left ventricle of rats with type 2 diabetes 2 as it is not accepted with 95% confidence.

Discussion

This study aimed to compare the two types of HIIT administration on two genes IGF-1 and IGF-1R expression and glucose levels in cardiomyopathic hearts in rats with type 2 diabetes.

Research findings suggested that there is no significant difference between an intense interval training type 1 (HIIT-1) and intense interval training type 2 (HIIT-2) on the IGF-1 gene expression in the left ventricle of rats with type 2 diabetes. A significant correlation was also found between glucose levels and IGF-1 gene expression after an intense interval training type 1 (HIIT-1) and intense interval training type 2 (HIIT-2) in the left ventricle of rats with type 2 diabetes.

The findings are consistent with previous research. Alizadeh et al. (2017) demonstrated that eight weeks of HIIT administration for 15 to 30 seconds with 90% VO2max and one minute of rest reduces fasting glucose levels and insulin resistance in adult male diabetic rats. The protocol of this training differs from the training protocol of the present study. Increased insulin sensitivity may be because of the of the omentin-1 gene expression from adipose tissue during HIIT. As well, this physical activity can strengthen and absorb glucose during and after training via various mechanisms. A total of 80 to 85% of blood sugar is consumed by skeletal muscle, and omentin plays its part in stimulating insulin receptors and glucose uptake in skeletal muscle. Therefore, a rise in the expression of omentin gene after training appears to be important in controlling hyperglycemia (20).

In a study making the mice diabetic with a high-fat diet after eight weeks of HIIT training along with two minutes of high frequency and two minutes of low frequency and continuous endurance training Khakdan et al. (2018) demonstrated a higher rate of left ventricular injection fraction and FS. As a consequence, HIIT specifically improved myocardial function and reduced the incidence of DCM. (21). Other related studies include the following:

In his study of 32 diabetic male mice of Sprago-Davoli race for 12 weeks and 5 sessions per week with HIIT and MI training, Coulson (2018) poin6ed out that glucose and insulin levels increased in diabetic animals, while training would normalize the level of these parameters. Plasma triglyceride levels were also found to have risen in diabetic animals. Previous research demonstrated that training reduces chronic low-grade inflammation, which characterizes metabolic diseases such as type 2 diabetes (T2DM).

Due to chronic myocardial inflammation, multifunctional pathways will lead to fibroblast proliferation and collagen production. These pathways are activated by several cytokines (TNF-α, IL-6, IL-1β) secreted by inflammatory cells and the central nervous system in response to the inflammatory state. In addition, advanced glycation accumulation ends. Products (AGEs) help cause myocardial inflammation and oxidative stress. Consequently, myocardial infarction leads to two symptoms of DCM, namely LV hypertrophy and fibrosis. In this case, the heart is not able to rest properly during diastole. Thus, fibrosis and hypertrophy are mechanical causes for diabetic heart damage (22).

Pirani et al. (2018) stated that doing a 10-week training course along with doing HIIT for 5 sessions per week by male Wistar rats increased IGF-1 in their hearts. Findings from studies investigating the IGF-1 response to chronic training also confirmed that both the intensity and duration of training determine the final level of IGF-1. Numerous studies have suggested that intense physical activity affects the IGF-1/IGF-BP axis. Generally speaking, the type of training is effective in taking IGF-1 (23). Studies have revealed that intense training affects the concentration of IGF-1 and the

results indicated that HIIT, like other models of intense training, leads to an increase in IGF-1 concentration. These results, as stated, were consistent with the results of the present study.

Conclusion

In sum, it was pointed out that HIIT training have a positive effect on glucose levels, IGF-1 gene expression. In the present study, HIIT increased IGF-1 in the left ventricle of diabetic rats compared to that in the diabetic control group. Also, the level of glucose in four weeks of HIIT was found to be lower than that in the diabetic control group, but this level was higher than the healthy control group. On the other hand, no significant difference was noted in IGF-1 gene expression and increased glucose during HIIT-1 or HIIT-2 administration. It appears that doing both types of training can yield the same effects on the plasma glucose IGF-1 gene expression in rats with type 2 diabetes. As a consequence, there is no need to use less rest time than activity time to get the desired result. Rest time is tantamount to intense activity time compared to when we rest for half an hour, resulting in less energy consumption.

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