ORGINAL ARTICLE

The Effect of Detraining High Intensity Interval Training on the Expression of AKT1 and mTORc1 Genes in the Left Ventricle of Diabetic Rats

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Received: 05 January 2020

Accepted: 28 April 2020

Published in June 2020

Abstract

Objective: The aim of this study was to investigate the effect of 6 weeks of detraining after 12 weeks of high intensity interval training (HIIT) on the expression of AKT1 and mTORc1 genes in the left ventricle of wistar diabetic rats.

Materials and Methods: Twenty-eight wistar male rats were selected as the study sample and were divided in four groups of healthy control, diabetic control, diabetic HIIT and diabetic HIIT + detraining. The HIIT period was 12 weeks and the detraining period was 6 weeks. Each session consisted of 30 minutes, which included running on a treadmill with one-minute repetitions and a two-minute active recovery between them. To measure AKT1 mRNA and mTORc1 mRNA by RT-Real time PCR, a single-step single step SYBR TAKARA kits from Takara Company was used according to the company's instruction.

Results: HIIT caused a significant increase in AKT1 gene expression (*P*-value= 0.001). AKT1 decreased with detraining that was not significant (*P*-value= 0.34) but it was still significantly higher than before training (*P*-value= 0.017). HIIT caused a significant increase in mTORc1 gene expression (*P*-value= 0.001) and although it decreased with detraining (*P*-value= 0.15) and it was no significantly higher than before training (*P*-value= 0.19).

Conclusion: HIIT led to increased expression of AKT1 and mTORc1 genes in type 2 diabetic rats, while also producing favorable changes in the cardiac structure of these rats. Also, 6 weeks of detraining did somewhat reduce these favorable changes.

Keywords: High intensity interval training, Detraining, AKT1, mTORc1, Diabetes

Introduction

Diabetes is a metabolic disorder that is characterized by increase in blood glucose due to deficiency of insulin secretion, resistance to insulin, or both. The prevalence of diabetes is expected to rapidly increase from 171 million individuals (2.8% of

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[DOI: 10.18502/ijdo.v12i1.3637]

the world's population) in 2000 to 366 million (4.4% of the world's population) by 2030 (1). Treatment goals in this disease include the decrease in insulin-resistance via nutrition control, exercise, drug treatment, and stimulation of insulin secretion (2). Sedentary habits are one of the main factors that develop Type 2 diabetes (3). Although aerobic exercise is generally recommended for people with diabetes and obesity, it should be noted that variety of training in terms of form, duration and intensity may have different effects.

High intensity interval training (HIIT) on the treadmill is an aerobic training. It may vary appetite peptides in people with type 2 diabetes. HIIT has been proposed as a time-efficient exercise intervention that may bring about similar benefits to moderate-intensity aerobic exercise. It has been reported that steady state exercise with duration of 30 min and moderate intensity in most days a week resulted in no fat reduction compared to HIIT, indicating high efficiency of HIIT for high fat oxidation and reducing fat tissue (4). HIIT is an appropriate training program for reducing body fat percent and for improving anthropometric indices in inactive young females (5). It has been demonstrated that HIIT can improve patient adherence to physical activity (6, 7) and numerous recent studies have also shown improvements in glycemic control following HIIT (8-15). The effects of HIIT on blood glucose could be partly mediated by improved skeletal muscle mitochondrial function, as it has been suggested by some authors (16).

On the other hand, cardiovascular disease is the leading cause of mortality in patients with diabetes mellitus (17). Some studies showed that there is probably a relationship between diabetes and left ventricular function (17). However, training can be considered as a protective factor for diabetic patient heart. The structural and functional changes in the left ventricle are greater than other parts of the heart during training (18,19). The aerobic training increases the left ventricular diameter and improves left ventricular diastolic function (20). Participation in intense regular training increased the thickness of the left ventricular wall and size of the cavities, which is a physiological change due to training (21).

The AKT / mTOR pathway is the main route that causes hypertrophy in training. Training causes cardiac growth, which is regulated by the GH / IGF axial signaling path via PI3k / AKT or AKT / mTOR. The activity of the AKT protein interacts with different intracellular substrates to regulate growth, metabolism and phosphorylation. The high expression of the IGF-1 receptor induces AKT activity, resulting in physiological hypertrophy by increasing calcium flow through the L-type calcium channel and SERCA. When AKT-1 is suppressed, the physiological growth and hemodynamic adaptations slow down. Glycogen synthase kinase-3 is an important negative regulator of protein synthesis that inhibited by AKT (22). The AKT / mTOR pathway contributes to the increase in muscle size and is activated with a variety of training (23). Meanwhile, the most important signaling pathway for left ventricular hypertrophy is the AKT / mTOR pathway, so that measuring the expression of the AKT and mTOR genes together with structural changes in the heart can provide useful information on the growth and improvement of cardiac conditions as a result of exercise training (24).

Some studies indicated that both morphologic and functional adaptations can decrease even after short detraining periods (25), it seems of interest to know whether the health promotion interventions benefits are maintained when detraining occurs, due to unexpected causes such as, illness, vacations, or others. In fact, despite evidence of physiological decline during detraining, there is not enough data suggesting how long the beneficial effects of training are maintained (26). The aim of this study was to investigate the effect of 6 weeks of detraining after 12 weeks of HIIT on the expression of AKT1 and mTORc1 genes in the left ventricle of wistar diabetic male rats.

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Materials and Methods

This is an experimental study. Twenty-eight wistar male rats (weight 248.32 ± 26.17 kg) were selected as the study sample. Animals were maintained at the standard condition. Ethics of work with animals was conducted according to the ethics committee of Iran University of Medical Sciences. After the rats were transferred to the laboratory, diabetes induction and introduction to exercise training were performed on the rodent treadmill and were divided into four groups of healthy control, diabetic control, diabetic HIIT and diabetic HIIT + detraining (7 rats in each group). In this study, mice were diabetic using nicotinamide and streptozotocin (STZ) (27). Nicotinamide (95 mg / kg dissolved in saline solution) was first injected intraperitoneally and after 15 minutes, 55 mg / kg STZ containing 0.1 molar of citrate buffer with a pH equal to ph. 4.5 was dissolved injected intraperitoneally. To detect diabetic rats, Five days after injection, a small drop of blood was injected into the tail of the animal on a glucometer strip and measured blood glucose and blood glucose levels of 126-400 mg / dl indicated their diabetes mellitus (28). The training period was 12 weeks and the detraining period was 6 weeks. HIIT program was for 12 weeks and 5 sessions per week. Each session consisted of 30 minutes, which included running on a treadmill with one-minute repetitions and a two-minute active recovery between them (29).

The training program was as follows:

- First week: repeats of one minute at 16 m / min and 2 minutes active recovery at 10 m / min between repetitions.
- Second and third weeks: repeats of one minute at 20 m / min and 2 minutes active recovery at 10 m / min between repetitions.
- Fourth and fifth weeks: repeats of one minute at 25 m / min and 2 minutes active recovery at 12 m / min between repetitions.
- Sixth and seventh weeks: repeats of one minute at 30 m / min and 2 minutes active recovery at 12 m / min between repetitions.
- Eighth and ninth weeks: repeats of one minute at 33 m / min and 2 minutes active recovery at 14 m / min between repetitions.
- Tenth to twelfth weeks: repeats of one minute at 36 m / min and 2 minutes active recovery at 14 m / min between repetitions.

After the intervention of each group, the rats were sacrificed and their heart tissue removed. To measure AKT1 mRNA and mTORc1 mRNA by RT-Real time PCR, a single-step single step SYBR TAKARA kits from Takara Company was used according to the company's instruction. The statistical analysis of the variables was done so that the values of each of the variables were first described using mean and standard deviation. Then, one-way ANOVA was used to compare the four groups. Significance level P-value$\leq$ 0.05 was considered. Also, SPSS software version 19 was used for statistical calculation.

Ethical considerations

This study was approved by the ethics committee of Islamic Azad University of Marvdasht Branch, Marvdasht, Iran. (code IR. IAU.M.REC.1399.003).

Results

The mean and standard deviation of the variables and results of one-way ANOVA test to compare the changes of variables between the four groups are summarized in Table 1. Also, the results of the tukey's post hoc test are presented in Table 2. Weight in the training group decreased significantly (P-value= 0.003), but it was increased by detraining, which was not significant (P-value= 0.094). Cardiac weight and left ventricular weight increased significantly with HIIT (P-value=0.001) and although significantly decreased with detraining (P-value= 0.001), it was still significantly higher than pre-training (P-value= 0.001). Ratio of cardiac weight to body weight increased significantly with HIIT (P-value= 0.001) and although significantly decreased with detraining (P-value= 0.029), it was still significantly higher than pre-training (P-value= 0.001). There was no significant

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difference between the four groups in ratio of left ventricle to cardiac weight (*P*-value= 0.31). HIIT caused a significant increase in ratio of left ventricle to body weight (*P*-value= 0.001) and although it decreased with detraining, it not significant (*P*-value= 0.10) but it was still significantly higher than before training (*P*-value= 0.001). HIIT caused a significant increase in AKT1 gene expression (*P*-value= 0.001) and although it decreased with detraining, it not significant (*P*-value= 0.34) but it was still significantly higher than before training (*P*-value= 0.017). HIIT caused a significant increase in mTORc1 gene expression (*P*-value= 0.001) and although it decreased with detraining, it not significant (*P*-value= 0.15) and it was no significantly higher than before training (*P*-value= 0.19).

Discussion

According to the findings of the present study, 12 weeks of HIIT led to increased expression of AKT1 and mTORc1 genes in type 2 diabetic rats, while also producing favorable changes in the cardiac structure of these rats. Also, 6 weeks of detraining did somewhat reduce these favorable changes. HIIT caused a significant increase in AKT1 and mTORc1 genes expression and they not significant decreased with detraining. After detraining, AKT1 was still significantly higher than before training but mTORc1 was no significantly higher than before training.

Launay et al. (2017) stated that HIIT is effective in improving muscle capacity and cardiac muscle proteins. In their study, they reported that 8 weeks of HIIT led to cardiac hypertrophy in rats by activating the IGF-I / mTOR / Akt pathway and down regulating the Smad2 / 3 pathways (30). The findings are present. Their findings confirm the present findings. Also, Lee et al. (2016) reported

Table1. Comparison of variables between four groups (ANOVA)

variables	Group	pre	Post	F	*P*-value
Weight (g)	Healthy control	247.71 (±29.21)	247.14 (±29.63)	10.39	0.001 *
	Diabetic control	229.42 (±20.35)	267.28 (±24.60)		
	Diabetic HIIT	274.57 (±13.35)	222.71 (±21.10)		
	Diabetic HIIT + detraining	246.57 (±19.38)	223.85 (±10.28)		
Cardiac weight (mg)	Healthy control	-	993.42 (±44.23)	58.27	0.001 *
	Diabetic control	-	922.14 (±31.86)		
	Diabetic HIIT	-	1130.42 (±20.49)		
	Diabetic HIIT + detraining	-	1006.71 (±14.34)		
Left ventricular weight (mg)	Healthy control	-	407 (±27.06)	30.33	0.001 *
	Diabetic control	-	378.14 (±16.09)		
	Diabetic HIIT	-	461.42 (±8.30)		
	Diabetic HIIT + detraining	-	419.14 (±6.56)		
Ratio of cardiac weight to body weight (mg/g)	Healthy control	-	4.06 (±0.44)	23.51	0.001 *
	Diabetic control	-	3.47 (±0.36)		
	Diabetic HIIT	-	5.10 (±0.43)		
	Diabetic HIIT + detraining	-	4.50 (±0.21)		
Ratio of left ventricle to cardiac weight (mg/mg)	Healthy control	-	0.409 (±0.013)	1.25	0.31
	Diabetic control	-	0.41 (±0.006)		
	Diabetic HIIT	-	0.408 (±0.006)		
	Diabetic HIIT + detraining	-	0.416 (±0.005)		
Ratio of left ventricle to body weight (mg/g)	Healthy control	-	1.66 (±0.20)	21.23	0.001 *
	Diabetic control	-	1.42 (±0.15)		
	Diabetic HIIT	-	2.08 (±0.17)		
	Diabetic HIIT + detraining	-	1.87 (±0.09)		
AKT1 (bp)	Healthy control	-	1.17 (±0.23)	8.82	0.001 *
	Diabetic control	-	0.30 (±0.13)		
	Diabetic HIIT	-	2.72 (±1.63)		
	Diabetic HIIT + detraining	-	1.88 (±0.78)		
mTORc1 (bp)	Healthy control	-	1.22 (±0.28)	7.08	0.001 *
	Diabetic control	-	0.50 (±0.17)		
	Diabetic HIIT	-	5.22 (±4.04)		
	Diabetic HIIT + detraining	-	2.77 (±0.87)		

* Significantly at the level of *P*-value≤ 0.05

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[DOI: 10.18502/ijdo.v12i1.3637]

similar findings with endurance training (31). But in contrast to the present findings, Sturgeon et al. (2015) found no significant changes in cardiac hypertrophy induced by AKT and mTOR signaling pathways in female rats after 2 months of training with moderate-intensity on treadmill (32). These results suggest that high intensity of exercise may be necessary for cardiac hypertrophy induced by training and that HIIT may be helpful. This is confirmed by the present findings.

In general, diabetes is associated with a high incidence of cardiovascular disease, which is the leading cause of death (33,34). Characteristics of chronic cardiac failure are decreased left ventricular function and loss of cardiomyocytes through apoptosis or necrosis (35). A diabetic heart has been shown to have an 85-fold increase in cardiomyocyte apoptosis (34). Exercise is an important non-pharmacological approach that can be used to improve quality of life and reduce pathological symptoms in patients with chronic heart failure (36). Studies have shown that exercise training reverses abnormal functional and molecular features of cardiac pathology (37-40). The underlying mechanism by which exercise prevents cardiac apoptosis in diabetes

Table2. Pair comparison between groups (tukey's post hoc test)

Variables	Paired comparison	*P*-value
Weight (g)	Healthy control - Diabetic control	0.65
	Healthy control - Diabetic HIIT	0.04 *
	Healthy control - Diabetic HIIT + detraining	0.98
	Diabetic control - Diabetic HIIT	0.003 *
	Diabetic control - Diabetic HIIT + detraining	0.45
	Diabetic HIIT - Diabetic HIIT + detraining	0.094
Cardiac weight (mg)	Healthy control - Diabetic control	0.001 *
	Healthy control - Diabetic HIIT	0.001 *
	Healthy control - Diabetic HIIT + detraining	0.84
	Diabetic control - Diabetic HIIT	0.001 *
	Diabetic control - Diabetic HIIT + detraining	0.001 *
	Diabetic HIIT - Diabetic HIIT + detraining	0.001 *
Left ventricular weight (mg)	Healthy control - Diabetic control	0.017 *
	Healthy control - Diabetic HIIT	0.001 *
	Healthy control - Diabetic HIIT + detraining	0.53
	Diabetic control - Diabetic HIIT	0.001 *
	Diabetic control - Diabetic HIIT + detraining	0.001 *
	Diabetic HIIT - Diabetic HIIT + detraining	0.001 *
Ratio of cardiac weight to body weight (mg/g)	Healthy control - Diabetic control	0.037 *
	Healthy control - Diabetic HIIT	0.001 *
	Healthy control - Diabetic HIIT + detraining	0.15
	Diabetic control - Diabetic HIIT	0.001 *
	Diabetic control - Diabetic HIIT + detraining	0.001 *
	Diabetic HIIT - Diabetic HIIT + detraining	0.029 *
Ratio of left ventricle to body weight (mg/g)	Healthy control - Diabetic control	0.051
	Healthy control - Diabetic HIIT	0.001 *
	Healthy control - Diabetic HIIT + detraining	0.097
	Diabetic control - Diabetic HIIT	0.001 *
	Diabetic control - Diabetic HIIT + detraining	0.001 *
	Diabetic HIIT - Diabetic HIIT + detraining	0.10
AKT1 (bp)	Healthy control - Diabetic control	0.31
	Healthy control - Diabetic HIIT	0.02 *
	Healthy control - Diabetic HIIT + detraining	0.47
	Diabetic control - Diabetic HIIT	0.001 *
	Diabetic control - Diabetic HIIT + detraining	0.017 *
	Diabetic HIIT - Diabetic HIIT + detraining	0.34
mTORc1 (bp)	Healthy control - Diabetic control	0.91
	Healthy control - Diabetic HIIT	0.007 *
	Healthy control - Diabetic HIIT + detraining	0.51
	Diabetic control - Diabetic HIIT	0.001 *
	Diabetic control - Diabetic HIIT + detraining	0.19
	Diabetic HIIT - Diabetic HIIT + detraining	0.15

* Significantly at the level of *P*-value≤ 0.05

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[DOI: 10.18502/ijdo.v12i1.3637]

remains poorly understood. The IGF-I / IGF-I-R axis and downstream signaling pathways PI3K and Akt have been shown to participate in mediating the critical response and apoptosis in cardiac tissue (41,42). In addition, the IGF-I / PI3K / AKT pathway is a critical mediator of exercise-induced cardiovascular physiology and Exercise has been shown to reverse abnormal functional and molecular features associated with cardiac pathology by increasing IGF-I or PI3K activity (37-40). Cheng et al. (2013) reported that IGF-I / PI3K / AKT pathways decreased in diabetic hearts, but increased significantly after training (43).

Among the PI3K-related protein kinase family, mTOR is a unique protein that plays a role in PI3K / Akt signaling. Although mTOR is coded by a single gene in mammals, binds to a specific regulatory protein in the form of two complexes containing mTORC1 and mTORC2 that both have distinct effects and mechanisms. Insulin and IGF-I stimulate the tyrosine kinase receptor, thereby activating the PI3K / AKT and Ras signaling pathways. Effective phosphorylated Akt and ERK1 / 2 kinases (1/2 extracellular signal regulated kinase) directly phosphorylate and inactivate the TSC1 / 2 heterodimer (1.2 stem cell sclerosis complex) (44,45). TSC1 / 2 functions as a GAP (activator protein of GTPase) for Rheb (Ras-enriched homolog in the brain) and decreases GTPase, Rheb-GAP. Thus, Rheb-GAP stimulates mTORC1 kinase activity and eventually insulin / IGF-I signaling activates mTORC1 activity via the PI3K / Akt signaling axis and consequently activates TSC1 / 2 (46). AKT can also activate mTORC1 kinase activity independently of TSC1 / 2 by direct phosphorylation and removal of PRAS40 (mTORC1 inhibitor) from RAPTOR (47). Among the downstream molecular processes of mTORC1, protein synthesis is the best characteristic, and two mTORC1 targets have been well identified in this regard (48). When mTORC1 is activated, S6K1 is phosphorylated, which promotes various cellular processes, including mRNA biogenesis, translation of ribosomal proteins, cell growth, and cell metabolism (49). Also, mTORC1 and S6K1 have an important negative feedback activity in inhibiting IRS-1 (substrate 1 insulin receptor) (50). Another target of mTORC1 is 4E-BP1 (elF4E-binding protein or eukaryotic translation inhibition factor 4E-binding protein), which accelerates its dissolution by elF4E, that it regenerates the conditions that synthesize protein (51). Hence, 4E-BP1 phosphorylation by mTORC1 is essential for initiating mRNA translation and protein synthesis. In addition, mTORC1 regulates cell growth and proliferation by inhibiting autophagy, which is an important process in maintaining cellular metabolic homeostasis (52).

Has been reported that HIIT with 85 to 90% VO2max results in a hypertrophic response in cardiomyocytes, which is briefly visible and reaches the plateau after about 2 months (53-55). The magnitude of cardiac hypertrophy depends on the intense of exercise because HIIT creates a response greater than moderate intensity exercise, with 14% reported for HIIT and 5% for moderate intensity training (53). Most studies (53,54) but not all (55) reported exercise-induced cardiac hypertrophy in rats. Concerning the mechanism of cardiac hypertrophy induced by HIIT, as with other exercises, it is dependent on the PI3K / AKT / mTOR signaling pathway (56) that is activated by IGF-I activation (57). Therefore, probably due to HIIT in type 2 diabetic rats, these changes lead to improved functional and structural features of the cardiac, possibly resulting in improved prevention of death from cardiac disease, which is a secondary disease in diabetics. In this regard, ostler et al. (2014) following HIIT showed modest improvements in glucose tolerance and basal AKT Ser473 phosphorylation (58).

In general, training adaptations decreased after a period of detraining (59,60), which in the present study also showed a decrease in adaptations of 12 weeks of HIIT after 6 weeks of detraining. However, after 12 weeks of HIIT, there was still some residual training adaptation that was significant for the

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[DOI: 10.18502/ijdo.v12i1.3637]

structural features of the cardiac compared with pre-training. In the present study, 12 weeks training led to a significant increase in the expression of these two genes. Also, although 6 weeks of detraining decreased the expression of the AKT1 and mTORc1 genes, the decrease was not statistically significant. Expression of both genes after 6 weeks of detraining after 12 weeks of HIIT was still higher than before training, which was significant for AKT1. It seems that if the detraining period was longer, the HIIT adaptations obtained would be fully restored to pre-training conditions. However, as stated above, the effect of detraining after HIIT or training on the expression of ALT1 and mTORc1 in diabetic rat cardiac has not been investigated, and the present study was performed for the first time. However, as there is not much research done in this area, further studies should be done by measuring other indices such as IGF-I, PI3K, etc. to obtain more reliable results.

Conclusions

Probably 12 weeks of HIIT can improve the structure of the cardiac and the expression of genes affecting it (AKT1 and mTORc1) in diabetic rats. But detraining after HIIT can lead to the loss of these training adaptations, which are not completely eliminated for up to 6 weeks.

Acknowledgements

This research is part of Farzaneh Soltanipour Jonaghani's doctoral dissertation at the Islamic Azad University, Tehran Central Branch. We would like to thank all those who helped us with this research.

Funding

This research was financially supported by Islamic Azad University, Central Tehran branch, Iran.

Conflict of Interest

The authors state that they have no conflict of interest.

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