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The Effect of Resistance Training on PI3K/mTORc1 Signaling in Left Ventricle of Diabetic Rats

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ABSTRACT

Background: Clinical evidence supports the influential role of genetic factors and intracellular signaling pathways in physiological cardiac hypertrophy. This study aimed to assess the response of the PI3K/mTORc1 signaling pathway in cardiac tissue to resistance training in obese rats with Type 2 Diabetes (T2D).

Materials and Methods: A total of 21 male Wistar rats (Mean±SD weight: 220±20 g) were obese by 6 weeks High-Fat Diet (HFD) and randomly assigned to 1) non-diabetic, 2) control T2D, and 3) exercise diabetic groups. T2D was induced by intraperitoneal injection of streptozotocin (30 mg/kg) for diabetic groups. The exercise group did the resistance exercise program (5 times per week for 6 weeks). After exercise training, PI3K and mTORc1 expression in the left ventricle and the ratio of the left ventricle to heart and heart to body weight were compared between groups. The obtained data were compared by 1-way Analysis of Variance (ANOVA) ($P<0.05$).

Results: Induction of diabetes resulted in significant decrease in all mentioned variables in control diabetic to non-diabetic rats (PI3K; P=0.021, mTORc1; P=0.004, left ventricle/heart weight; P=0.045, heart/body weight; P=0.035). Significant increase was observed in all variables (PI3K; P=0.028, mTORc1; P=0.015, left ventricular/heart weight; P=0.002, heart/body weight; P=0.001) in response to resistance training compared to the control rat.

Conclusion: Based on our results, cardiac hypertrophy in studied diabetic rats can be attributed to improved PI3K/mTORc1 signaling in response to resistance training. Exploring the exact mechanisms responsible for these changes in response to exercise requires further molecular-cellular studies.

Introduction

More than 90% of metabolic disorders are attributed to Type 2 Diabetes (T2D) [1], so its prevalence is expected to increase to more than 300 million by 2025 [2]. Complications of this disease include not only hyperglycemia and insulin resistance but also many cardiovascular diseases such as coronary heart disease, hypertension, pathological hypertrophy, and atrophy of the heart or heart cavities are also consequences of this disease [2]. Cardiovascular disease is the leading cause

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of death in diabetic patients. Patients with diabetes are at risk for hypertension, atherogenesis, coronary artery disease, and myocardial infarction. Some research has shown a possible link between diabetes and left ventricular dysfunction [3], so that control of myocardial dysfunction is inversely related to diabetes [4].

In patients with T2D, excessive stiffness of the left ventricular wall during the diastolic phase prevents left ventricular regeneration after myocardial infarction, which ultimately increases the left ventricular filling stage pressure in both Heart Failure (HF) diseases and decreases the ventricular ejection fraction and with left ventricular ejection fraction [5]. Although pathological hypertrophy occurs in patients with hypertension or valvular heart disease, the physiological hypertrophy of the heart seen in athletes is associated with adaptations such as angiogenesis and transfusion of blood more than the heart [6]. Thus, pathological cardiac hypertrophy is associated with interstitial fibrosis and myocyte apoptosis, which is not seen in physiological hypertrophy [7]. Although these abnormalities occur in response to metabolic and hormonal disorders, the role of transcription components and genetic factors should not be overlooked. Thus, PI3K may manage the physiological hypertrophy process of cardiac myocytes due to its effect on downstream components such as AKT1 and mTORc1 [8].

However, the main mechanism responsible for cardiac hypertrophy is not yet fully diagnosed. T2D reduces or inhibits physiological hypertrophy by reducing the PI3K expression in cardiac myocytes [9, 10], although this process is manifested by a decrease in mTORc1 expression [11]. On the other hand, increasing the activity of the PI3K/AKT1/mTORc1 signaling pathway leads to protein synthesis or hypertrophy [11].

Exercise training is a protective factor for the heart of diabetics. Numerous studies have shown that structural and functional changes in the left ventricle are greater than in other heart parts during exercise [11-13]. Obert et al. reported that aerobic training increased left ventricular diameter and improved left ventricular diastole function [14]. In another study, Rawlins et al. also found that engaging in intense regular exercise increases the thickness of the left ventricular wall and the size of cavities, a physiological change resulting from exercise [15]. Some studies have also reported an increase in signaling pathways leading to mTORc1, such as increased AKT/mTORc pathway activity in response to exercise stimulating skeletal muscle hypertrophy [16]. However, to date, no study has investigated the effect of exercise on the PI3K/mTORc1 pathway in cardiac tissue. Therefore, this study aimed to assess the impact of resistance training on PI3K and mTORc1 expression as well as the left ventricle to heart weight ratio and heart to body weight ratio in diabetic rats.

Materials and Methods

Experimental animals

A total of 21 rats (ten-week-old, mean weight: 220 ± 30 g) were prepared from the animal house of Baqiyatallah University, Tehran, Iran. Then, they were randomly divided into 3 groups: 1) non-diabetic, 2) control T2D, 3) exercise T2D. Animals were provided with a High-Fat Diet (HFD), and they were maintained in standardized conditions (12-h light/dark cycle, 25±2°C, and humidity of 45%-55%). All rats were left for a week for acclimatization before the commencement of the protocol.

Ethical considerations

This study was approved by the Research Ethics Committee of the Islamic Azad University of Borujerd Branch, Borujerd, Iran (Ethical Code: IR.IAU.B.REC.1400.014) and carried out in accordance with CPCSEA (The Committee for the Purpose of Control and Supervision of Experiments on Animals) guidelines.

Induction of obesity and type 2 diabetes

After getting acquainted with the laboratory environment, all rats were fed a high-fat diet for 6 weeks to become obese [17]. Then, 7 rats were selected as the non-diabetic obese group (health group, n=7). The rest received a single intraperitoneal injection of 30 mg/kg streptozotocin to become T2D [13]. Diabetic rats were divided into exercise (resistance training, n=7) or control (n=7) groups. Hyperglycemia was confirmed by elevated blood glucose one week after injection, and only animals with fasting blood glucose of 150-400 mg/dL were selected as T2D [18].

Resistance training protocol

After ensuring diabetic induction, the rats in the exercise group were trained to climb on a stepladder (a 1-m vertical ladder with 26 steps and a slope of 80%) without resistance 6 times in 3 exercise sessions to learn how to exercise. Then, they completed resistance training that lasted 6 weeks for 5 days in weeks. To warm up and cool down, the rats were allowed to climb up and down the ladder 2 times without any resistance before and after the workout.

Table 1. Resistance training protocol based on the percentage of body weight

Time	First Week	Second Week	Third Week	Fourth Week	Fifth and Sixth Weeks
Resistance (body weight %)	30	50	70	90	100

Each exercise session was performed in 5 sets, 4 repetitions on each set, and the resistance was increased through attaching a weight to rats' tails. The resting periods between sets and repetitions were 3 min and 45 s, respectively. The resistance gradually increased during training intervention (Table 1) [17]. Finally, all rats were dissected 48 hours after the last exercise session and following overnight fasting (10-12 hours fasted). The rats of the non-diabetic and diabetic control groups were not included in the exercise program.

Sample collection and bochemical assay

Forty-eight hours after the last session, the fasted rats were anesthetized through intraperitoneal injection of 2% xylocaine (10 mg/kg) along with 10% ketamine (50 mg/kg). Then they were dissected [19]. After anesthesia, blood samples were obtained through cardiac puncture. Afterward, their heart tissues and the left ventricles were removed. Their left ventricles were immersed in RNA to analyze and determine PI3K and mTOREc1 expression. In addition, the glucose amount was determined by the glucose oxidase method (Pars Azmoon kit). Insulin was determined by ELISA (Demeditec, Germany) and the intra-assay and inter-assay coefficients of the method were 2.6% and 2.88%, respectively.

RNA extraction/real time-PCR

To purify RNA, 20 mg of left ventricular tissue was ground using a mortar and pestle, and extraction was performed employing the RNeasy Protect Mini Kit (Qiagen Inc. in Germany) [17]. In this stage, the One-Step SYBR PrimeScript RT-PCR Kit (Takara Bio Inc. in Japan) was employed according to the manufacturer's protocol to prepare the reaction product. The thermal cycle used for the Rotor-Gene Q instrument was as follows: 42˚C for 20 min; 95˚C for two min; and 40 cycles with 94˚C for 10 s and 60˚C for 40 s. Temperatures from 50˚C to 99˚C were used to the melting curve after the PCR to study the characteristics of the primers (Table 2).

Statistical analysis

The obtained data are expressed as Mean±SD and analyzed in SPSS software v. 15. One-way ANOVA and Tukey post hoc test were used for comparing the variables between the studied groups. P values less than 0.05 were considered statistically significant.

Results

Bodyweight, fasting blood glucose, and serum insulin of groups are presented in Table 3. One-way ANOVA was used to compare variables between groups. Based on the results, significant differences were found in body weight ($P<0.05$), the ratio of the left ventricle to heart weight ($P<0.05$), and the ratio of the left ventricle to body weight ($P<0.05$). Based on the results of the Tukey test, resistance training in the exercise group led to a significant increase in left ventricle/heart weight ratio compared to non-diabetic ($P=0.002$) and control diabetic ($P=0.001$) groups (Figure 1). On the other hand, the heart/body weight ratio also increased significantly in the exercise rats compared to the non-diabetic ($P=0.001$) and control diabetic ($P=0.001$) groups (Figure 2).

Induction of diabetes decreased PI3K and mTORc1 expression. So, PI3K and mTORc1 expression in the control diabetic group was significantly reduced compared with the non-diabetic group ($P=0.001$). Resistance training increased mTORc1 expression in the diabetic exercise compared with

Table 2. Primer sequence

Genes	Primer Sequence	Product Size	Tm	Gene Bank
PI3K	Forward: ACTGAGATGGAGACACGGAAC Reverse: GCATCCAAGGGTCCAGTTAGTG	159 bp	60	NM_001191052.1
mTORc1	Forward: TGCAGCCTGACCAATGATGTG Reverse: CTTGTGTCCGGCAGCATCATC	159 bp	60	NM_001191052.1
RNA Polymerase II	Forward: ACTTTGATGACGTGGAGGAGGAC Reverse: GTTGGCCTGCGGTCGTTC	164 bp	60	XM_008759265.1

Table 3. Mean±SD of body weight and diabetic determinants of studied groups

Groups	Non-diabetic	Control Diabetic	Resistance Diabetic
Body weight (g)	401±13	387±9	415±6
Heart weight (g)	1.147±0.501	1.033±0.0407	1.232±0.0115
Left ventricle (g)	0.4115±0.0434	0.3480±0.0120	0.5453±0.0140
Glucose (mg/dL)	122±5	300±12	189±17
Insulin (µIU/mL)	9.23±0.64	8.97±0.22	6.58±0.15

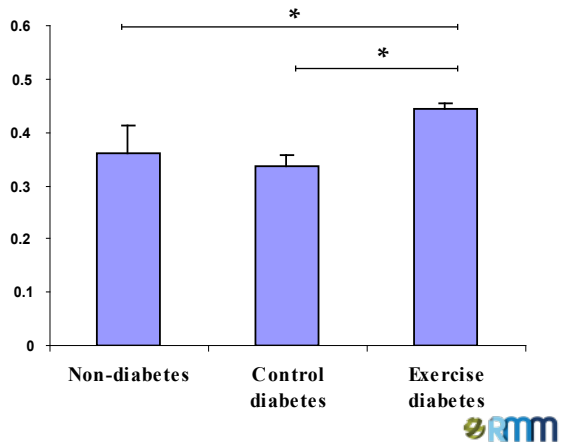

Figure 1. The left ventricular/heart weight ratio of studied groups

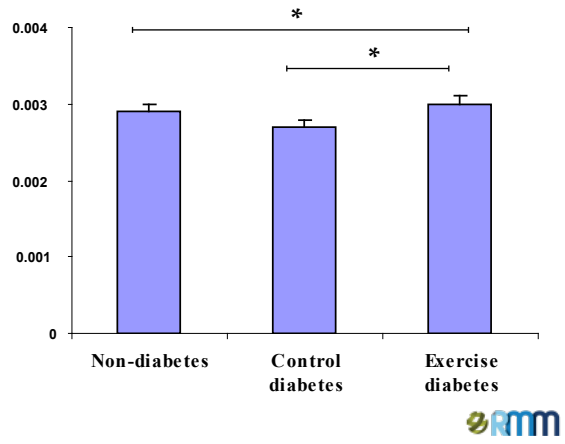

Figure 2. The heart/body weight ratio of studied groups

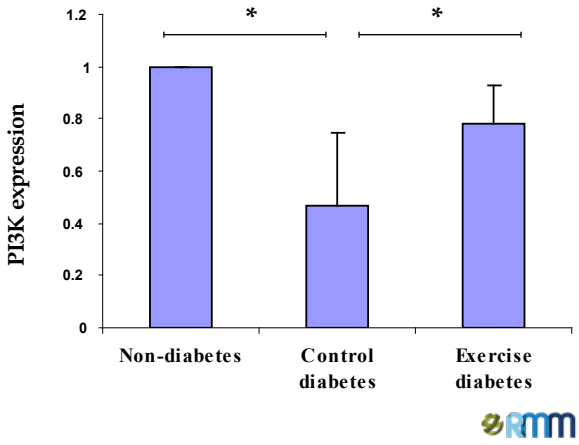

Figure 3. The change pattern of PI3K expression in left ventricular of studied groups

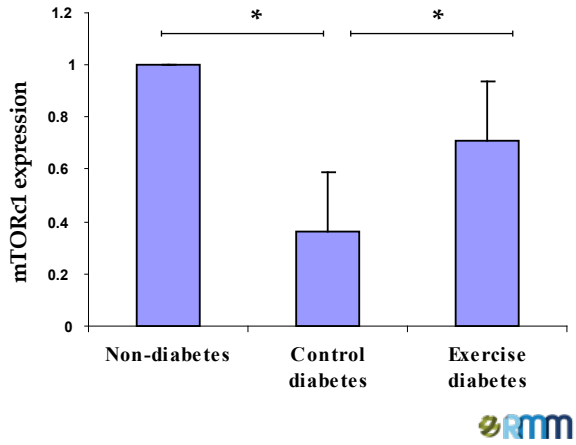

Figure 4. The change pattern of mTORc1 expression in left ventricular of studied groups

the control diabetic rats (P=0.015) (Figure 3). Based on the available findings, resistance exercise also increased PI3K expression compared to the control diabetic rats (P=0.028), and this increase was so significant that the difference in PI3K expression between the exercise and non-diabetic groups became insignificant (P=0.115) (Figure 4).

Discussion

Increased expression of PI3K and mTORc1 in response to resistance training is the study's main finding. In other words, 6 weeks of resistance training (5 sessions per week) increased the expression of PI3K and mTORc1 in the left ventricles of the studied rats. This improvement was also associated with an increase in the ratio of the left ventricle to heart weight and left ventricle to body weight in the studied rats.

In this regard, although no study has been conducted on the effect of exercise on PI3K expression in diabetic rats, some studies have reported the response of mTORc1 to exercise training. Mirsepasi et al. reported an increase in

mTORc1 expression in the heart tissue of diabetic rats in response to long-term interval training [20]. Bacurau et al. also noted that aerobic exercise reduces muscle atrophy in mice with heart failure by increasing the activity of the IGF-I/Akt/mTORc signaling pathway [21]. Liao et al. concluded that 8 weeks of moderate-intensity exercise leads to cardiac hypertrophy in mice by increasing the expression of AKT1 and mTORc1 [22]. However, Sturgeon et al. reported no change in expression of AKT1 and mTORc1 in response to 2 months of treadmill aerobic exercise in mice [23].

On the other hand, increased activity (PI3K/P110α) in the heart of mice in response to exercise training has been reported by some researchers [24]. Increased PI3K activity in skeletal muscle of healthy individuals and individuals with insulin resistance has also been reported in response to endurance training with an intensity of 60% to 70% maximal oxygen consumption [25, 26]. These findings are reported while other studies have shown no effect of exercise training on PI3K and other signaling pathways leading to hypertrophy [27, 28]. Researchers believe that abnormal functional and cellular-molecular pathological features of the heart are reversed by increased activity of the IGF-1 and PI3K-dependent signaling pathways following exercise [29, 30]. The researchers also noted that although these signaling pathways are weakened in response to diabetes, they are significantly increased in response to exercise [30].

Researchers believe that the induction of T2D leads to a 10% to 20% reduction in VO_2max [31]. On the other hand, exercise leads to a 2- to 6-fold increase in resting cardiac output. Most researchers have attributed to hypertrophy and increased contractility of cardiac cavities, especially the left ventricle [31]. Functional and structural adaptations in the heart muscle depend on the type of exercise. Studies have shown that adaptation resulting from strength and endurance training is different in the heart and heart cavities [32]. Aerobic training leads to extroverted hypertrophy in response to volume overload [33]. In this regard, Fathi et al. reported an increase in left ventricular diastolic diameter in response to endurance training [34].

In our study, resistance training was associated with an increase in left ventricle/heart weight ratio and left ventricle/body weight ratio compared with the diabetic control group or the non-diabetic group. Some researchers have attributed this improvement to intracranial hypertrophy of the heart cavity in response to the stress load induced by resistance training [35]. Some researchers have suggested that intense exercise, even at lower volumes, leads to better effects on myocardial muscle structure due to stronger messaging of transcription factors than light exercise. This process can also be seen in interval exercises [36, 37].

The above evidence and our findings emphasize the cardiac hypertrophy of resistance training combined with increased expression of genes involved in this process. Thus, cardiac and left ventricular hypertrophy of diabetic rats in response to this training method may be attributed to improving the PI3K/signaling pathway. Decreased expression of these two transcription factors in response to induction of T2D in our study also supports the influential role of this signaling pathway in cardiac hypertrophy or muscle hypertrophy. In this context, it has been shown that induction of diabetes in mice increases the expression of MIR221 in cardiac tissue [38].

PI3K lies upstream of mTOR, a critical positive regulator of protein synthesis and cell growth. PI3K/AKT/mTOR signaling axis is a key intracellular transduction pathway. PI3K can be activated by cytokines, growth factors, and hormones as an extracellular signal than a second messenger binding of the Akt PH area that activates Akt [39]. Activated Akt promotes the Glycogen Synthase Kinase-3β (GSK-3β), phosphorylation of mTOR, and other downstream substrates that play a wide range of biological effects, such as promoting cell survival and anti-apoptosis [40]. Phosphor-mTOR initiates the 70 kD ribosomal protein S6 kinase (p70S6k1) and phosphorylated translation of eukaryotic initiation factor 4E Binding Protein 1 (4EBP1). mTOR, specifically via phosphorylation of p70S6K1 and 4EBP1, plays a key role in regulating the rate of protein synthesis [41, 42]. On the other hand, increased expression of MIR221 by inhibition of AKT leads to inhibition of cardiac hypertrophy, especially in the left ventricle. In other words, MIR221 overexpression leads to the inhibition of myocardial hypertrophy by inhibiting the AKT1/PI3k signaling pathway [43]. On the other hand, it has been revealed that physiological hypertrophy of the heart depends on the activity of PI3K-dependent signaling pathways [44].

In summary, the PI3K/mTORc1 signaling pathway and other downstream pathways such as PI3K/AKT play a regulatory role in cell growth, cell survival, metabolism, and left ventricular hypertrophy [45]. According to the results of our study, cardiac hypertrophy especially left ventricle in response to resistance exercise, may be attributed to increased PI3K and mTORc1 expression or PI3K/mTORc1 signaling pathway. In this regard, Palabiyik et al. have pointed out that long-term swimming training leads to increased expression of genes involved

in the PI3K/AKT/mTORc signaling pathway. These researchers attributed exercise-induced cardiac hypertrophy to improving this signaling pathway [46]. However, because of the unique role of AKT1 in this signaling pathway, one of the research limitations was the lack of measuring AKT1 expression.

Conclusion

Resistance training leads to cardiac hypertrophy with increased expression of PI3K and mTORc1 in the left ventricle in diabetes rats. Based on the present study findings and citing previous evidence, this improvement can be attributed to the increased activity of the PI3K/mTORc1 signaling pathway in heart tissue in response to this type of exercise. Further studies are required to understand other mechanisms responsible for signaling pathways affecting cardiac hypertrophy in response to exercise.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Islamic Azad University, Borujerd Branch (Code: IR.IAU.B.REC.1400.014).

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Authors contribution's

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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