The Effect of 6 Weeks Resistance Training and High-Intensity Interval Training on Glut-4 Gene Expression of Diabetic Rats

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Abstract

Objective: GLUT4 glucose transporter content and glucose transport capacity are closely correlated in muscle. The purpose of current study was to evaluate the effect of 6 weeks of resistance training and High-Intensity Interval Training (HITT) on Glut-4 gene expression in type 2 diabetes mellitus (T2DM) by high fat diet and STZ.

Materials and Methods: This study was done on 32 male Wistar in Baqiyatallah University of Medical Sciences-Tehran. The study sample consisted of 32 male Wistar 10 week old weighting 220 ± 20 gr which were divided into 4 obese groups. One diabetic group had to do resistance training and another group did HIIT. One more diabetic group and the healthy group did not do any activities. At the end, the amount of their left ventricular GLUT-4 was measured. Independent t-test and one way ANOVA were used to examine the results.

Results: The expression of Glut-4 in the left ventricle of diabetic rats was 0.72 lower than that of the non-diabetic group, due to T2DM induction (*P*-value:0.029). There was a significant difference between the groups in expressing Glut-4 in the left ventricle. The post hoc test confirmed a significant increase in the expression of Glut-4 in the resistance and HIIT group compared to the control group (*P*-value:0.017 and *P*-value:0.05).

Conclusion: However, there was no significant difference in expression of Glut-4 between the two groups of resistance and HIIT. Our findings showed that T2DM patients with cardiovascular disease can improve their problem by performing physical activity.

Keywords: Resistance training, HIIT, GLUT-4, Type 2 diabetes

Introduction

Normal glucose homeostasis is the result of a balance between the appearance of glucose in the blood and its cellular uptake and use (1). These processes are controlled by the action of hormones (insulin and glucagon) and by a family of membrane proteins (2,3). The function of these glucose transport proteins (GLUTs) is modified in derangements of glucose homeostasis such as diabetes and obesity (4,5). GLUT4 is expressed as the major transporter only in tissues which

glucose uptake is stimulated by insulin (like cardiac muscle) (6,7). There is a close correlation between GLUT4 protein concentration and maximally stimulated glucose transport (8,9). Furthermore, GLUT4 protein concentration and maximally stimulated glucose transport activity vary in parallel in response to different adaptive stimuli (9-12).

A major stimulus that induces an adaptive increase in GLUT4 is exercise. This adaptation occurs in 6-12 weeks programs of running or swimming (10-14).

The pool of GLUT4 vesicles that responds to insulin is biochemically distinct from GLUT4 vesicle populations that redistribute to the plasma membrane under other stimuli such as exercise (15-17).

GLUT4 mRNA expression is largely restricted to brown and white adipose tissue, skeletal muscle, and heart. Glucose uptake via GLUT4 in these tissues is used for very different purposes related to the tissue's function.

GLUT4 gene expression is also a matter to up and down regulation depending on the physiologic state of the organism. Changes in GLUT4 gene expression are observed in physiologic states of altered glucose homeostasis. In general, GLUT4 mRNA expression is reduced in severe insulin deficiency such as STZ-induced diabetes and nutritional deprivations such as starvation (18,19). These changes in steady-state GLUT4 mRNA levels are tissue specific. For example, changes in GLUT4 mRNA expression occur much more rapidly in adipose tissue than skeletal muscle (20). Chronic fasting markedly reduces GLUT4 mRNA levels in adipose tissue, but has little or no effect on GLUT4 mRNA in skeletal muscle (21). These tissue-specific physiologic adaptations are consistent with the tissue-specific fates of GLUT4-dependent glucose uptake in these tissues. Specifically, muscle must retain its pool of GLUT4 so that it can call on GLUT4 to respond to exercise and muscle contraction.

Changes in steady state levels of GLUT4 mRNA could potentially be the result of changes in either the rate of synthesis of GLUT4 mRNA (gene transcription) or stability of messenger RNA. Nuclear run on assays measuring the rate of GLUT4 mRNA transcription demonstrate that transcription is decreased in both adipose tissue and skeletal muscle in STZ-induced diabetic animals (22,23), while the rate of the GLUT4 gene transcription in skeletal muscle of fasted animals is increased (23). Thus, changes in GLUT4 mRNA steady state levels reflect changes in the rate of mRNA synthesis.

In contrast to the down regulation of GLUT4 which is observed in insulin deficiency and fasting, GLUT4 expression is increased at the transcriptional level by endurance exercise (23). The increase in GLUT4 gene expression in response to exercise is rapid, occurring after only one session after aerobic exercise (24). This increase is 1.5-2 folds which is enough to modify carbohydrate metabolism (24). After cessation of endurance training, GLUT4 expression reverts to normal levels in two to four days (25,26).

The study aim was to recognize genetic variations and their possible changes in response to exercise.

Materials and Methods

The present study is experimental and fundamental research. The study was done in Baqiyatallah University of Medical Sciences in Tehran. Thirty two male Wistar 10 weeks old weighting 220 ± 20 gr, which were selected and divided into 4 obese groups (3 diabetic type 2 and 1 healthy groups).

Protocol method

For induction of type 2 diabetes, a high-fat diet for 6 weeks followed by intraperitoneal injection of STZ solution in citrate buffer with PH = 4.5 (30 mg / kg). For the preparation of high-fat foods in standard diets of rats purchased from Pars and Food Company, 1% cholesterol powder and 1% 100% pure corn oil were added. One week after diabetes induction, fasting blood sugar (FBS) was

measured. FBS level between 150 and 400 mg / dL was considered as type 2 diabetes (27).
All of the rats were kept under controlled light conditions (12 hours of light and 12 hours of darkness, 6 am and 6 o'clock) with temperature (22 ± 3 °C) and humidity in the range of 30-60. Three rats were kept in Plexiglas cages with a lid and dimensions of 25 by 27 by 43 cm, so that they can freely access standard water and food.

Study groups

Male Wistar rats were randomly divided into 4 groups including 3 diabetic type 2 diabetics (HIIT diabetic group, resistant diabetic group, and diabetic control group) and a healthy non-diabetic group.
The HIIT periodic diabetic group contain 8 rats, 10 weeks old, and from the 16th week of a period of HIIT six weeks 5 sessions of 30 minutes per week in the form of running on treadmill with 40-second repetitions and active 2-minute rest between each repeat (28). All rats were dissected 48 hours after the last training session.
The second group (diabetic group with resistance training): This group consisted of 8 male, 10 week old male Wistar rats who were diabetic with high-fat diet and STZ, and from the 16th week in a course of resistance training for 6 weeks, 5 sessions Weekly in the form of 5 sets with 4 replays per set. The interval between sets was 2 minutes and the intervals between repetitions per set were 30 seconds. All mice were described 48 hours after the last training session. The application of the resistance to close the weight to the tail of the rats is equivalent to different percentages of body weight during the training period.
Diabetic control group: The group consisted of 8 male 10 week old male Wistar rats that were diabetic during 6 weeks of high-fat diet and STZ infusion and continued to use high-fat diet until the end of the study. Finally, they were described with rats in other groups.
Healthy group: The group consisted of 8 male 10 week old male Wistar rats that were obese over a 6-week high-fat diet and continued to use high-fat diet until the end of the study. Finally, they were described with rats in other groups.
There is a Reverse Primer in the kit. But the Forward primer is designed with iodine. In fact, the Forward primer is the same as the mature micro RNA sequence, but should be checked for the melting temperature (Tm), so that if its melting temperature is not matched with the Reverse primer, changes to its structure are given. After designing a primer by a geneticist, the order was made to make the company a pioneer, and was prepared after a week. In addition, the RNA-polymeras2 gene was used as control gene. Table 1,2 shows the pattern of primers.
RNA extraction: RNA was extracted from the pancreatic tissue by the Rneasy Protect Kit (QIAGEN) kit according to the company's instructions. We scraped 20 milligrams of tissue from scalpel into microtiops and then extracted the RNA using the RNeasy Protect kit in accordance with the instructions of the German manufacturer.

Statistical analysis

Descriptive statistics were used to describe the data and draw charts, to compare the groups, independent t-test and one way ANOVA were used. For completing additional tests, a follow-up test of LSD was performed as needed. The significance level will be considered as α=5%. All statistical analyzes were performed using SPSS software version 22.

Table 1. High intensity interval training protocol

Weeks	Running repetitions	Running speed (meter per min)	Steep percent	Recovery speed (meter per min)
1	8 rep.	25	5	10
2	10 rep.	25	10	10
3	10 rep.	28	10	10
4	10 rep.	32	10	10
5	10 rep.	35	10	10
6	10 rep.	35	10	10

Table 2. Resistance Training Load

Weeks	Resistance (Percentage of Body weight)
1	30
2	50
3	70
4	90
5	100
6	100

Results

Based on independent T-test to compare diabetic and non-diabetic control groups, the mean expression of GLUT-4 (in the left ventricle of diabetic rats was reduced by 0.72 ± 0.27 to non-diabetic group (*P*-value:0.029).

The results of one-way ANOVA test showed that there was a significant difference between the groups in the expression of GLUT-4 in the left ventricle (*P*-value:0.04), so that the post hoc test of LSD had a significant increase of GLUT-4 expression in the group with resistance training was confirmed (*P*-value: 0.017). On the other hand, based on the findings of the post-test LSD, HIIT exercise also led to a significant increase in expression of GLUT-4 compared to the control group (*P*-value:0.050). However, there was no significant difference in expression of GLUT-4 between the two groups of resistance (2.06±0.91) and HIIT (1.84±0.89) (*P*-value: 0.572) (Figure 1).

Discussion

The results of this study indicated that 6 weeks HIIT and resistance training resulted in expression of GLUT-4 receptor expression in the left ventricle of type 2 diabetic rats. Glut-4 is expressed in the heart, skeletal muscle and adipose tissue (29,30), where it is responsible for decreasing plasma glucose levels after a meal (31).

Previous study examined the effect of swimming training on Glut-4 gene expression in diabetic rats. The results showed a significant increase in the expression of the Glut-4 gene (32).

One study demonstrated increase in Glut-4 expression in male Wistar rats in response to 6-week swimming training (33). Also an increase in Glut-4 expression in mice that swam for 5 days was showed (34).

The results of all these studies are consistent with the results of this study. Although not well understood, what exercises affect the presence of Glut-4, but it has recently been suggested that Glut-4 plays an important role in regulating glucose and insulin.

Therefore, it is likely that due to increased insulin receptor substrate due to exercise activity, a positive feedback would be generated and increased transporter protein. Another hypothesis to increase Glut-4 expression in response to exercise may be Galanin effects. Galanin is a nerve gland peptide and an important hormone in insulin sensitivity fluctuations (35).

One study noted that Galanin increased by

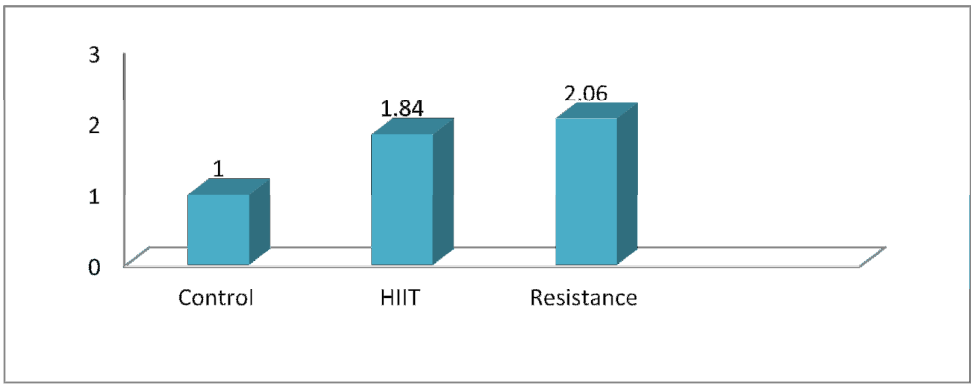

Figure 1. Relative levels of GLUT-4 expression in the studied groups

physical exercise in mice. In this study, insulin sensitivity and Glut-4 expression also increased (36). According to these results, Glut-4 expression may be associated with increased Galanin levels.

Finally, Glut-4 increases due to exercise may be due to the effects of Glut-4 mRNA. SLC2A4 gene prescription is activated by two major factors: the increasing myositis factor 2 (MEF2) and the increasing factor Glut-4 (GEF) (35,36). On the other hand, AMPK protein activity as a result of muscle contraction requires HDAC5 phosphorylation, which results in secretion of MEF2 (37).

HIIT increases the expression of Glut-4 in skeletal muscle more than low intensity exercise by activating both calcium-dependent messenger pathways and the AMP enabled protein kinase pathway (AMPK). However, the increase of Glut-4 gene expression is dependent on the amount of energy consumed, more than that it is affected by single mode exercise (38).

It was reported that levels of GLUT-4 mRNA increased due to physical activity and decreased during insulin deficiency (39), and these changes were due to variations in the level of Glut-4 genetic enzymes (40).

Insulin acts by stimulating the transfer of Glut-4 containing vesicles from intracellular sources to the plasma membrane, resulting in a rapid and immediate increase in glucose transmission (41). Glut-4 gene expression is regulated by complex mechanisms that are exposed to tissue-specific and also hormonal metabolism (42). Thus, Glut-4 expression in skeletal and cardiac muscles is disrupted in contravening normal conditions such as hypothyroidism during pregnancy (43,44).

The results of some studies showed large amounts of multiplier increases at the cell level, including Glut-4, depend on the response to exercise or muscle contractions in the evaluation method (45). As a result of the exercise, the amount of Glut-4 protein in the large sarcolema vesicles increases approximately twice (46).

A relative study stated that there was no difference in the expression of Glut-4 in samples that had been swallowed for 4 weeks (47-48). These results are not consistent with the results of the present study. Possible reasons for mismatching are the type of exercise, the intensity of exercise, the duration of exercise, the population tested and sampling methods.

However, it is suggested that molecular mechanisms are responsible of these results, which may depend on the type of muscle.

Conclusions

These results point to the important role and expression of Glut-4 expression and function in absorbing glucose, followed by the reduction of cardiovascular risk associated with high sugar. The adaptive increase in GLUT-4 may also help to explain these findings that a few days of exercise training can result in a significant enhancement of insulin action on glucose disposal (49).

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