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The Effect of 6 Weeks Resistance Training and HITT on GLP-1 Gene Expression of Diabetic Rats

Hossein Kalhor[1], Maghsoud Peeri[2*], Hasan Matin Homaee[3], Mojtaba Izadi[2]

1. PhD student of Exercise physiology, Islamic Azad University, Central Tehran branch, Tehran, Iran.
2. Associate Professor, Islamic Azad University, Central Tehran branch, Tehran, Iran.
3. Assistant Professor, Islamic Azad University, Saveh branch, Saveh, Iran.

***Correspondence:**
Maghsoud Peeri, Associate Professor, Islamic Azad University, Central Tehran Branch, Tehran, Iran.
Tel: (98) 218 856 2484
Email: m.peeri@iauctb.ac.ir

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Abstract

Objective: Cardiovascular diseases are the main reason of the death in type 2 diabetic patients. The purpose of this study was to evaluate the effect of 6 weeks of resistance training and HITT (High Intensity Interval Training) on GLP-1 gene expression in type 2 diabetes mellitus.

Materials and Methods: For this study, male Wistar rats of Baqiyatallah University of Medical Sciences in Tehran were used as statistical population. The statistical samples consisted of 32 male Wistar 10 weeks old weighing 220 ± 20 gr and were divided into 4 obese groups (3 diabetic type 2 and 1 healthy groups). Groups were diabetic obstruction, resistance exercises, diabetic obesity and HITT exercises. Independent T-test and one way ANOVA were used to examine the results.

Results: The results showed that the expression of GLP-1R in the left ventricle of diabetic rats was 0.6% lower than that of the non-diabetic group, due to type 2 diabetes induction. There was a significant difference between the groups in expressing GLP-1R in the left ventricle. The post hoc test confirmed a significant increase in the expression of GLP-1R in the resistance and Interval group compared to the control group. However, there was no significant difference in expression of GLP-1R between the two groups.

Conclusion: With regard to the results of this study and other studies that have an effect on the proper administration of Glp-1 and its receptor on the heart, it can be proven to heart patients that they can recover by performing physical activity.

Keywords: Resistance training, HIIT (High-Intensity Interval Training), GLP-1R (Glucagon-Like Peptide 1- receptor), Diabetes Mellitus, Type 2

Introduction

The incidence of obesity is associated with the increase of cardiovascular disease, metabolic syndrome, diabetes and insulin resistance. The World Health Organization (WHO) noted the rapid increase in the prevalence of obesity and its complications as the main health problems in the world (1). Obesity is one of the main causes of mortality in developed countries. In developing countries, the prevalence of

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obesity is rising especially in high socio-economic status (2-5). Obesity and type 2 diabetes mellitus (T2DM) are known as a global epidemic. Apart from genetic and hereditary factors, scientific evidence clearly supports obesity as the most important factor in the onset of T2DM. Obesity also exacerbates the prevalence of T2DM due to increased insulin resistance and blood glucose (6).

Cardiovascular diseases are the main reason of the death in T2DM patients (7). Glucagon-like peptide (GLP-1) 1 is a physiologic hormone secreted in response to food intake by intestinal L cells (8,9). GLP-1 increases the sense of sourness after eating in thin individuals as well as in obese people (10,11). The researchers showed that gastro-intestinal polypeptide is a powerful stimulant for the secretion of GLP1 (12). On the other hand, stimuli of the nervous system by some stimuli are other reasons for the secretion of GLP-1 (13,14). The activation of the nervous system caused by food intake has also been addressed as a factor in the early release of GLP1 (15). Physical activity is one of the ways to stimulate the sympathetic nervous system (16). Clinical studies have pointed out the lower levels of GLP-1 in patients with coronary artery disease (17). Direct correlation of GLP-1 plasma levels and left ventricular diastolic function has been reported (18). Another study found that GLP-1 agonists were able to improve and increase the effective parameters in the left ventricular contractility, such as increasing the peak power and speed of left ventricular systolic cells as well as factors affecting the left ventricular function in T2DM patients (19). Use of GLP-1 agonists lead to increased systolic and diastolic function and reduces the oxidative stress in mice with ischemic heart disease (20). Also, expression of GLP-1 receptor was isolated in the heart of dogs, as well as in myocardium of coronary muscle and coronary endothelium in rats. GLP-1 levels in response to Exercise increases. But 60 minutes of walking on the treadmill did not change GLP-1 response after meals. Also, Novak et al. (2013) showed that 60 minutes of moderate intensity aerobic exercise (55-60% Vo2 peak) did not change GLP-1 levels (21). Lee et al. showed that high-intensity Interval exercises, as compared with low intensity Interval exercises, could increase GLP-1 levels and improve glycemic index and body composition in T2DM patients (22). The purpose of this study was to evaluate the effect of 6 weeks of resistance training and HITT (High Intensity Interval Training) on GLP-1 gene expression in type 2 diabetes mellitus.

Materials and Methods

The experimental study was conducted on Baqiyatallah University of Medical Sciences in Tehran. The study sample were 32 male Wistar rats 10 weeks old weighing 220 ± 20 gr, which were divided into 4 obese groups (3 T2DM and 1 healthy groups).

For induction of T2DM, a high-fat diet for 6 weeks followed by injection of freshly prepared STZ solution in citrate buffer with PH = 4.5 was performed intraperitoneal at a dose of 30 mg / kg. For the preparation of high-fat foods in standard diets of rats purchased from Parsand Food Company, 1% cholesterol powder and 1% 100% pure corn oil were added. One week after diabetes induction, fasting blood sugar (FBS) was measured and glucose levels between 150 and 400 mg / dL were considered as type 2 diabetes (23).

All of the rats were kept under controlled light conditions (12 hours of light and 12 hours of darkness) with temperature 22 ± 3 ° C and humidity in the range of 30-60. Male Wistar rats were randomly divided into 4 groups including 3 type 2 diabetics (HIIT diabetic group, resistant diabetic group, and diabetic control group) and a healthy non-diabetic group.

The first group (HIIT Interval diabetic group) was from 8 male 10 weeks old male Wistar rats who were diabetic with high-fat diet and STZ, and from the 16th week of a period of high intensity interval training six weeks 5 sessions of 30 minutes per week in the form of

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running on treadmill with 40-second repetitions and active 2 minutes rest between each repeat (24). All the rats were described 48 hours after the last training session.

The second group (diabetic group with resistance training): This group consisted of 8 male, 10 weeks 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.

Group 3: (Diabetic control group): The group consisted of 8 male 10 weeks 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.

Group 4: (healthy group): The group consisted of 8 male 10 weeks old male Wistar rats that were observed 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 microRNA 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-polymerz2 gene was used as control gene. Table 1 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 and to compare the groups in the variables, independent t-test and one way ANOVA were used. For completing additional tests, a post hoc test of LSD was performed if needed. All statistical analyzes were performed using SPSS 22.

Results

Based on independent T-test (comparison between two diabetic and non-diabetic control groups): Due to the induction of T2DM, the expression of GLP-1R in the left ventricle of diabetic rats was reduced by 0.62 ± 0.34 to non-diabetic group (*P*-value: 0.018). (Table 2)

The results of one-way ANOVA test showed that there was a significant difference between the groups in the expression of GLP-R in the left ventricle (*P*-value: 0.035) , so that the post hoc test of LSD had a significant increase the expression of GLP-R in the resistance group was confirmed (*P*-value: 0.016).

On the other hand, based on the findings of the post-test LSD, interval exercise also led to a significant increase in expression of GLP-R compared to the control group (*P*-value: 0.04). However, there was no significant difference in expression of GLP-R between the two groups of resistance and Intervention (*P*-value: 0.61) (Tables 1, Diagram 1).

Table 1. Changes in GLP-1R gene expression in response to training interventions in training groups compared to the diabetic control group

Group	GLP-1R gene expression
Diabetic control group	2.09±1.09
Training interventions groups	2.32±0.97

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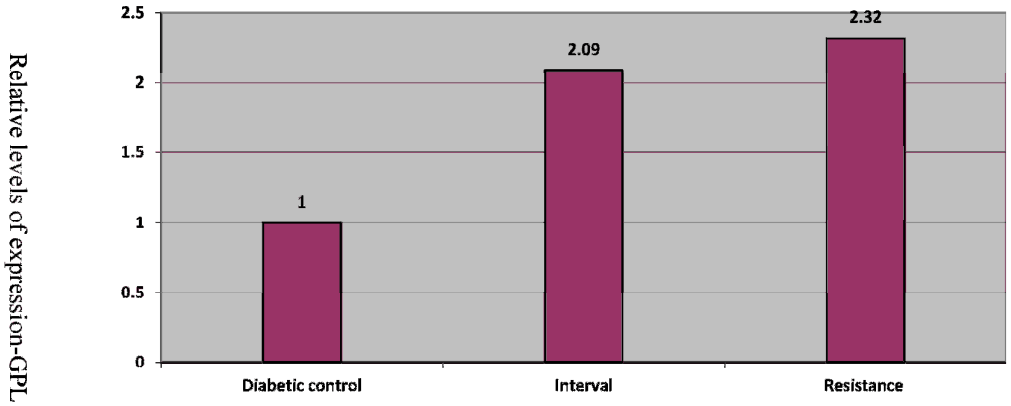

Figure 1. Relative levels of GLP-1R expression in the studied groups

Discussion

The results of this study indicated that 6 weeks interval and resistance training resulted in expression of Glp1 receptor expression in the left ventricle of T2DM rats.

GLP-1 is a major marker and actor in glucose homeostasis. GLP-1 has multiple positive effects in blood glucose control. An immediate increase in this peptide stimulates the secretion of glucose-dependent insulin. Also GLP-1 inhibits glucagon secretion and cell death.

As GLP1 has essential effects on the body's organs, several factors play a role in the production and use of hormones as well as in the expression of GLp1 receptors. However, due to the fact that the study on the effect of physical activity on the expression of the GLP1 gene in the left ventricle of the heart has not been carried out, and according to the results of the investigations by Timar et al. (25), Steppan et al (26) and Calabro et al. (27) Showed that GLP-1 direct and complete cardiac function is dependent on GLP-1 receptor, so the results of the research can be generalized and also discussed with the results of this study. The present study was conducted to identify GLP1 as a heart protector against possible dangers of T2DM. Therefore, several studies have been conducted to determine the effect of stimuli or external interventions in order to improve the factors determining T2DM. In addition, apart from drug interventions, the role of diet modification and different patterns of exercise and physical activity as non-pharmacological treatments in preventing of diabetes or reducing its severity by increasing GLp-1 in patients with diabetes has always been at the center of attention of researchers in science health and well-being. However, according to different training methods, differences in the duration, severity and frequency of training sessions, the type of population studied in terms of weight and age range, or individual differences and life patterns before the intervention, are contradictory findings in this regard. Despite this contradiction, it has been recognized for decades that exercise along with diet and drug use is an effective way of managing diabetes.

Martinez et al. (28) stated that increasing the probability of GLP-1 receptor activation is a natural response to exercise.

Accordingly, Steppan (26) and Ahima (29) demonstrated isolated expression of GLP-1 receptor in the hearts of dogs, as well as in myocardium of coronary muscle and coronary endothelium in rats. This increase in the expression of GLP-1 receptor is consistent with the results of the present study and suggests that specific stimuli express the gene expression of this receptor. Meanwhile, Martinez et al. (28) indicated that GLP-1 levels of exercise increased with exercise, also Adam et al. (30), Martinez et al. (28), Ueda et al. (31) and Levine et al. (32) stated in separate studies that GLP-1 levels increased in

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response to exercise. The results of the research are consistent with the results of this study. In another study, Martinez et al. (28) showed that GLP-1 plasma concentration increased after 60 minutes of intermittent biking in 65% of maximum heart rate. Also, Ueda et al. (31) in a study that performed subjects with high intensity (75%) and moderate (50%) on a fixed bike for 30 minutes increased GLP-1 in plasma in both groups, which indicates that there is no difference in the intensity of GLP-1 in this study. Meanwhile, GLP-1, 30 minutes after testing were still at high levels (31). In another study, O'Connor et al. (33) examined the effect of 2 hours of long running on 60% Vo2max treadmill. The results showed that GLP-1 levels increased significantly in healthy subjects (33).

Regarding the variability of the training variables in the type, duration, and intensity of exercise, and the different responses of the body organs to each of these variables, it is possible that the reason for the inconsistency of the results of various researches from this perspective may arise. In support of this issue, Lee et al. examined the effect of high intensity interval (80% heart rate reserve) and low intensity (45% heart rate) on GLP-1 levels in diabetic patients (22). The results showed that high intensity interval exercises compared with low intensity Interval exercises could increase GLP-1 levels and improve glycemic index and body composition in T2DM patients. It is well known that the reason for the discrepancy between the results of low frequency interval exercise and the present study is the difference in intensity of activity.

Melissa et al. showed that 60 minutes of medium-intensity aerobic activity (55-60% Vo2 peak) did not change GLP-1 levels (34). This research is not consistent with the results of this study. According to the above, it is likely that the difference in the type of exercise is incompatible with the present study. In fact, perhaps the difference is the difference in aerobic exercises versus Interval exercises

Also, Dekker et al. reported that 60 minutes of walking on the treadmill did not change GLP-1 response after meal (35). In interpreting this conclusion, which was not consistent with our results, it should be noted that the possibility of intolerance by subjects and low intensity of work may be due to the lack of alignment. Because walking in aerobic exercise, compared to a high intensity Interval exercise or resistance training, in which heart rate reaches its high levels, does not have the intensity required for GLP-1 tangible secretion.

Abolfathi and the coworkers, investigated the effect of moderate acute anaerobic exercise on changes in GLP-1 levels in diabetic women (36). The results showed that activity on GLP-1 levels in serum, glucose and insulin is not significant.

Another study by Eshghi the coworkers (2013) with the effect of aerobic exercise with metformin and without metformin on plasma quinone in T2DM patients found that exercise did not affect GLP-1 levels (37). This study was not consistent with the results of the present study and the reasons for the inconsistency, duration, intensity and time of the training and the population were tested.

Since one of the main activities of the GLP-1 hormone and, consequently, the GLP-1 receptor is reduced and absorbed by plasma glucose, plasma glucose levels can also be a good indicator of GLP-1 levels. GLP-1 receptor activation typically coincides with the increase in insulin (e.g. post-meal), therefore, Sigal et al. (1995), in his research, showed that the production of GLP-1 receptor in the body naturally responded the increase in blood glucose levels prevents hepatic glucose production, and here the role of GLP-1 receptor in regulating glucose production of glucose during insulin transplantation is physiological (38). Due to the diabetic nature of the present study and high blood glucose levels, it may be due to the similarity of the results of the research.

In the same vein, Sigal et al. stated that GLP-1 activity in the brain, especially in the

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hypothalamus, can regulate acute glucose production and consumption (38). The question now is whether the GLP-1 receptor regulates the absorption of glucose in the absence of increased insulin levels? Exercise is a good answer to this question because exercise with an insulin-independent mechanism regulates the absorption of muscle glucose. However, during exercise, arterial glucose levels were not significantly different in GLP1. This was not due to defective absorption of muscle glucose; this case was in the hyper insulin of the normal muscle and even increased in the diaphragm. The results of Sigal's study showed that exercise-induced hyperglycemia in GLP1 / G rats was associated with an inadequate increase in liver glucose production (38). Liver glucose production during moderate-intensity physical activity usually increases to match glucose uptake by contraction muscle.

All of the above studies confirmed the results of the present study, which were based on the increase of GLP-1 levels, which is consistent with the present study. Clinical studies showed that intravenous GLP-1 increases cardiac efficiency and function against coronary artery disease and heart failure and ischemic / recurrent injury (22-29). For example, patients with chronic heart failure experienced a significant improvement in left ventricular injections, VO2max and 6 minutes walking distance after GLP-1 injection (28).

Animal studies indicated that GLP-1 intravenous and intra coronary and GLP-1 receptor agonists reduced infarct rate and increased left ventricular function following ischemia (20,39).

Intravenous GLP-1 in animals with heart failure has been shown to improve several cardiac function parameters, such as left ventricular injections, cardiac output and impulse volume (39).

Although GLP-1 receptor dependent pathways may also be involved in beneficial cardiovascular effects, the findings suggest that GLP-1 non-receptor pathways play a role in direct cardiac activity. It was also found that the use of the DPP4 inhibitor eliminated GLP-1 in the GLP-1 receptor mice, but this was not the case in the heart of ordinary mice with GLP-1 (39). This indicates that in the absence of the GLP-1 receptor, direct GLP-1 cardiac activity is performed, but the full and complete effects of GLP-1 are dependent on the GLP-1 receptor. Similar effects of GLP-1 receptor agonists have been observed in large animal models (12,20).

When GLP-1 was injected into coronary heart disease of rats, or injected into the vein of dogs with heart failure, it increased the absorption of myocardial glucose that was associated with some cellular signaling cascades. However, in the isolated heart of the rats, this insulin-dependent effect occurs at 30 minutes, while in dogs, a longer-lasting injection of about 6 hours was required (12). This difference is likely to be due to the fact that the longer injection time for systemic splicing has been used to achieve concentrations equal to those found in intra coronary injection.

Conclusions

In summary, the potential physiological mechanisms for the therapeutic functions of GLP-1 to increase the function of the left ventricle and reduce the rate of infarction include: 1. Inotropic effect (contraction force) 2. Effect on substrate metabolism and 3. Effect on coronary blood flow (19,39-41).

Therefore, according to the results of most studies, the proper effect of GLP-1 and its receptor on the heart, and according to the results of this study, showed that the increase in receptor of this polypeptide in the left ventricle of the heart has been shown by physical activity.

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